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No. 1

THE RELIABILITY OF THE ELECTRICAL DIAGNOSIS OF TETANY

WITH ESPECIAL CONSIDERATION OF THE ELECTRICAL VALUES FOUND IN
NORMAL CHILDREN *

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BALTIMORE

The first electrical diagnoses of tetany in children were made on well marked clinical cases. The electrical values obtained in these were much lower than those found in children free from tetany. It was later discovered that some children who showed no clinical evidences of tetany gave electrical values nearly if not quite so low as those found in cases of clinical tetany. Such children were said to suffer from latent tetany, the diagnosis being based wholly on the electrical reactions.¹

With this extension of the conception of tetany as an active and as a latent disease of infancy and childhood, the diagnosis of it has, especially with older children, come to rest on a less secure foundation. There have been no electrical standards established for normal children beyond the period of infancy, it having apparently been assumed that the values established for infants are applicable to older children as well. A study of the reactions in older children shows almost at once that this assumption is unjustifiable.

Even with infants, also, the determination of what is normal and what is abnormal offers at times great difficulties. Therefore, I have studied the reactions of infants and older children with and without tetany in order to determine the reliability of the electrical diagnosis of this disease and, especially with older children, to establish the standards for the normal and the deviations from this which enable us to recognize the presence of tetany.

The Development of the Conception of Tetany.—Many of the symptoms which we now recognize as belonging to tetany were first described in infants that were teething. Increased irritability, abnormal

* Submitted for publication April 15, 1916.

* From the Harriet Lane Home and from the Department of Pediatrics of the Johns Hopkins University.

1. The chief justification for this conception and diagnosis of latent tetany is to be found in the fact that some of these children with low electrical values later develop unmistakable clinical symptoms of tetany.

contractions of the muscles, transient spasms, and, finally, convulsions, were thought to be more or less normal accompaniments of dentition. It was not until a century ago that physicians studied certain of these symptoms more carefully and began to recognize their abnormal character. One by one they were described, at first as independent entities and then as different manifestations of one underlying disease.

James Hamilton² in 1809 gave a beautiful description of spasm of the larynx and spoke of it as the most formidable symptom, except convulsions, which occurs during dentition. In 1816 George Kellie³ of Leith wrote at some length on a form of swelling of the backs of the hands and feet and on a spasmodic affection of the thumbs and toes which commonly accompanied it. Underwood, he said, had earlier described this condition, regarding it as of no importance, since it went away upon the eruption of the teeth; but to Kellie it seemed rather to constitute "a part of a disease of a somewhat more serious and striking nature." In the next year James Johnson⁴ of Philadelphia applied the term "carpopedal spasm" to this condition. It occurred, in his case, in association with transient spasmodic affections of the muscles of respiration.

In 1819 J. Cheyne⁵ differentiated clearly between hydrocephalus and laryngospasm. He said: "The pathognomonick of this disease is a crowing inspiration, with purple complexion, not followed by cough. In some cases . . . attended, not merely with a permanent clenching of the hand upon the thumb, but also with a very remarkable fixed spasm of the toes, particularly the great toe, which gives a look of swelled deformity to the upper part of the foot." He spoke also of the associated convulsions.

John North⁶ referred to the syndrome as one generally recognized, and Marshall Hall⁷ described the symptoms in a complete manner and attributed their appearance to reflex irritation of the central nervous system from teething and the presence of indigestible food residue in the gastro-intestinal tract.

The names of the earlier workers are, it will be noted, all British or American. Their views seem to have had little influence on French teaching; they were, however, accepted in Germany and there further elaborated. Then attention became centered upon details of symptomatology and etiology and the broader view that grouped together under

2. Hamilton, James: *Hints on the Treatment of the Principal Diseases of Infants*, 1813.

3. Kellie, George: *Notes on the Swelling of the Tops of the Hands and Feet, etc.*, *Edinburgh Med. and Surg. Jour.*, 1816.

4. Johnson, James: *Med.-Chir. Jour.*, Philadelphia, 1817, iii, 448.

5. Cheyne, J.: *Essays on Hydrocephalus, or Water in the Brain*, Ed. 2, 1819.

6. North, John: *Practical Observations on the Convulsions of Infants*, 1826.

7. Hall, Marshall: *Diseases and Derangements of the Nervous System*, 1842.

one head the conditions of laryngospasm and nonepileptic convulsions of childhood was almost forgotten for many years.

It is to Cheadle⁸ and those working with him that we owe the reestablishment of the old views of tetany after they had remained in obscurity for many years. "Laryngospasmus, tetany and convulsions," said Cheadle in 1887, "are different expressions of the same constitutional morbid state, are associated especially with the first two years of life, with the period of rickets and with the period of dentition." He designated this morbid constitution as "a state of erethism," in which the central nervous system is in a condition of abnormal excitability. He considered this condition and tetany of adults one and the same disease, with, however, this difference: in the adult muscular contraction predominates in the picture, in childhood convulsions and laryngospasm predominate. Abercrombie⁹ had noted "facial irritability" as a new symptom. Stewart,¹⁰ an American, reported in 1889 the presence of increased electrical excitability (Erb's phenomenon) in the tetany of childhood.

Escherich¹¹ (1890) found that mechanical excitability of the nerves, especially the facial phenomenon, was regularly present in laryngospasm, and that Trousseau's sign and spontaneous contractions seldom failed. In association with von Wagner, he demonstrated at that time the presence in the infant of galvanic electrical hyperirritability of the nerves, similar to that found in the tetany of adults. Moreover, he found that this electrical hyperirritability came and went with the attacks of laryngospasm and that as the attack passed away the spontaneous contractions disappeared first, then the Trousseau phenomenon, next the laryngospasm, and finally the electrical hyperexcitability.

The views of Escherich met at first with much opposition, but they were soon confirmed by reports from other sources. In the next year (1891) Escherich reported his observations on nearly three hundred cases. Since that time the contributions have dealt, for the most part, with details of diagnosis, etiology and treatment, and need not be mentioned here.

The Electrical Diagnosis of Tetany.—The presence of increased electrical excitability in the nerves of adults suffering from tetany—the so-called Erb's phenomenon—was noted by Erb in 1878. The first

8. Cheadle: Pathology and Treatment of Laryngismus, Tetany and Convulsions, Lancet, London, 1887, i, 919.

9. Abercrombie: On Tetany in Young Children, London, 1880.

10. Stewart: Tetany, Am. Jour. Sc., December, 1889, cited after Escherich.

11. Escherich: Idiopathische Tetanie im Kindesalter, Wien klin. Wehnschr., 1890, iii, 769; Begriff und Vorkommen der Tetanie im Kindesalter, Berl. klin. Wehnschr., 1897, xxxiv, 861; Die Tetanie der Kinder, Vienna and Leipsic, 1909, p. 10.

report of the presence of similar heightened electrical excitability in children suffering from tetany came from the American physician, Stewart, in 1889.

The first extensive study of Erb's phenomenon in the tetany of children under three years of age was made in the clinic at Graz, in 1890, by Escherich and his associate von Wagner. Ganghofner,¹² Hauser,¹³ Kalischer,¹⁴ Burkhardt,¹⁵ von Pirquet,¹⁶ and others supplemented these studies. The nerves most commonly selected for examination have been the median nerve (stimulated in the bicipital fossa) and the peroneal nerve (stimulated near the head of the fibula—Erb's point). The earlier investigators anesthetized their patients, thinking that restlessness might interfere with satisfactory readings; later workers have not found this necessary. As the change in the electrical excitability of the nerves in tetany is a general one, affecting all the peripheral nerves,¹⁷ it is possible, by examining one nerve, to determine the condition of the peripheral nervous system as a whole. It is necessary, however, to have some table of the values to be expected in normal children for use as a comparison.

Stintzing¹⁸ in 1886 prepared tables showing the range of values found for each of the peripheral nerves in normal adults, but no similar table has been compiled for infants and children. The Stintzing tables for adults give the cathodal closing (C. C. C.) values only. That the determination of the cathodal closing value alone is not sufficient in the case of infants and young children is shown by a brief review of the development of our knowledge of galvanic electrical reactions in children. The work of Escherich, Ganghofner, Burkhardt, Kalischer, Thiemich and Mann,¹⁹ and finally of von Pirquet, is of especial interest.

Escherich found what he considered abnormally low values for the C. C. C. (cathodal closing contraction) and the C. C. Te. (cathodal closing tetanus) in the few patients he examined in 1890. He spoke also of the occasional appearance of anodal opening tetanus, though the strength of current required to produce it was not given.

12. Ganghofner: Ueber Tetanie im Kindesalter, *Ztschr. f. Heilk.*, 1891, xii, 447.

13. Hauser: Ueber Tetanie der Kinder, *Berl. med. Wchnschr.*, 1896, xxxiii, 782.

14. Kalischer: *Jahrb. f. Kinderh.*, 1896, xlii, 386.

15. Burkhardt: Die Tetanie im Kindesalter, *Cor.—Bl. f. schweiz. Aerzte*, 1893, xxiii, 23.

16. Von Pirquet: Die Anodische Uebererregbarkeit der Säuglinge, *Wien. med. Wchnschr.*, 1907, lvii, 14.

17. This assertion, though commonly accepted, is questioned by some authors; consult Borrutau-Mann: *Handbuch der electro-medizinische Technik*, Leipzig, 1909, ii, 384.

18. Stintzing: Ueber elektrodiagnostische Grenzwerte, *Deutsch. Arch. f. klin. Med.*, 1886, xxxix, 76.

19. Thiemich and Mann: *Monatschr. f. Psychiat. u. Neurol.*, 1899, vii, 14; *Jahrb. f. Kinderh.*, 1900, li, 99.

Ganghofner examined thirteen cases and found the cathodal closing values low in all, with a return to higher values as the symptoms of tetany vanished.

Burkhardt in 1893 reported a typical case of tetany in a 2½ year old child, with increased galvanic excitability.

Hauser in 1896 was the first to dispense with chloroform anesthesia. He examined 280 children, ages not given, with various diseases, and testing the median and ulner nerves for the cathodal closing contraction and cathodal closing tetanus, found C. C. C. values ranging from 0.2 to 0.5 milliamperes and C. C. Te. from a few ma. to 16 ma. As a result of his study he asserted that increased electrical excitability of the nerves was the most constant and important symptom of tetany. Oddly enough, he did not observe this phenomenon in most of the cases of laryngospasm that he examined. Kalischer reported similar findings in the same year.

In 1897 Escherich published the results of later examinations made by him without anesthesia. He found what he considered to be an increased electrical excitability in all cases of tetany examined by him, and found, also, that this heightened electrical excitability preceded the appearance of spasms, and lasted weeks or months after these had disappeared. Especially important appeared to him the lowering of the C. C. Te. values. The nerve examined in this study is not mentioned.

In the same year (1897) Thiemich made an important contribution to the subject by determining what he considered the normal values for children in what we may call the tetany age, and by calling attention to the significance of the early appearance of cathodal *opening* contractions (C. O. C.). Stintzing had already determined the normal range of values for the cathodal closing contraction (C. C. C.) in adults. The Westphals,²⁰ father and son, studying the C. C. C. only, had shown that much higher values obtain in newly born infants. Thiemich and Mann examined fifty-six children whom they believed free from tetany and, averaging their findings, obtained the following results:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
Children under 8 weeks of age.....	2.6	2.9	5.1	9.3
Children over 8 weeks of age.....	1.4	2.2	3.6	8.2

The nerve examined was the median, the point of stimulation being at the end of the bicipital fossa just above the bend of the elbow. The ages of the children were not given, nor were the actual findings from which the averages were obtained. There is evidence that the

20. Westphal, A.: Die electrischen Erregbarkeitsverhältnisse des peripheren Nervensystems des Menschen im jugendlichen Zustande und ihre Beziehungen zu dem anatomischen Bau desselben, Arch. f. Psychiat., 1894, xxvi, 1; Westphal, C.: Neurol. Centralb., 1886, v, 6.

children were all under three years of age. Thiemich and Mann thus obtained results that were more precise than any that had previously been recorded.

They then examined children of this age who were suffering from tetany, latent and active, and recorded similarly the electrical values found in them. They noted, in addition to low values for the C. C. C. (cathodal closing contraction), a preponderance of A. O. C. $<$ A. C. C., anodal opening contractions appearing with less current than anodal closing contractions, and especially the appearance of C. O. C. with a current of less than 5 ma.

This last observation, the appearance of C. O. C. under 5 ma., Thiemich thought characteristic of tetanoid conditions of the nervous system; indeed he emphatically insisted that such a reaction was necessary for the diagnosis of tetany.

Ganghofner in 1904 reported the results of a few examinations. In the main he confirmed Thiemich's conclusions, but he believed that cases of undoubted clinical tetany may exist in which the cathodal opening contraction may be above 5 ma. (C. O. C. $>$ 5 ma.), and that he had seen children (ages not stated) in whom the C. O. C. occurred with a current less than 5 ma., yet who neither before nor after the examination ever presented any clinical signs of tetany.

In reviewing the reports of all the earlier observers the reader is struck with the fact that the ages of the children examined are rarely given. In some instances one may infer that the age was under three years, for example, in Thiemich and Mann's work; as a rule the reader is left in doubt. Much more precise is the statement of the next contributor of importance, von Pirquet.

Von Pirquet in 1907 made systematic and repeated examinations on twenty-four children in the infant section of the Vienna clinic, through periods ranging from one month to a year. The oldest of these children appears to have been under two years of age. Two of the twenty-four developed definite signs of clinical tetany at some time during the year. As the result of his study von Pirquet offered the following corrections to the work of Thiemich and Mann, and gave as normal values for infants under 2 years of age as follows:

C. C. C.	A. C. C.	A. O. C.	C. O. C.
3	>5	>5	>5
(exceptionally 1 to 5)	or <5		

These values were obtained from the peroneal nerve.²¹ As is indicated, von Pirquet found that the value of the anodal closing contrac-

21. Von Pirquet stated that he made comparative studies on the peroneal and median nerves and that his results showed approximately equal values for the opening contractions on the two nerves, and distinctly lower values in the median nerve for closing contractions.

tion varied and that it often fluctuated from day to day. The anodal opening value, on the other hand, he found remarkably constant:

Von Pirquet drew the following conclusions:

1. Normal infants present only closing contractions under 5 ma. when examined with the galvanic current.

2. The appearance of an anodal opening contraction under 5 ma., when unaccompanied by a cathodal opening contraction or cathodal closing tetanus under 5 ma., is characteristic of a low grade of hyperexcitability that may be termed anodal hyperexcitability.

3. Anodal hyperexcitability is a precursor of cathodal hyperexcitability, which is indicated by the appearance of cathodal closing tetanus or a cathodal opening contraction under 5 ma.

This work is the last important contribution to the development of the subject. In addition to giving a more precise statement regarding the electrical values in children under 2 years of age, von Pirquet introduced the conception of anodal hyperexcitability. Anodal hyperexcitability, he found, preceded the appearance of cathodal hyperexcitability, accompanied it, and was present for a time after the disappearance of the latter. It was present during the late spring of one year in one half of the infants in the Vienna Hospital, and it was in this group that the two cases of clinical tetany appeared; therefore, he regarded this condition, anodal hyperexcitability, as a sign of latent tetany.²² The development of active clinical, or manifest, tetany in his two cases was accompanied by the appearance of cathodal hyperexcitability (C. C. < 5 ma.).

Von Pirquet stated distinctly that his observations were made upon infants. He believed that the values for normal infants are approximately those given by Thiemich and Mann for children in the first

22. The term "latent tetany" seems to have been first used by Erb. In his chapter on Tetany in Ziemssen's Handbuch it is stated that repeated examination by him of two cases had shown that there existed a condition of increased electrical excitability, a fact earlier affirmed by several observers, notably by Benedict and Kussmahl; and that "the greatest increase of excitability coincided with the time of the best marked and most frequent attacks of tetany and there was a decrease in the excitability as they became less frequent; and finally, when the patient had completely recovered, the electrical excitability was found to be approximately normal. A distinct parallelism could thus be demonstrated to exist between the occurrence of spasms and the increase of electrical excitability" . . . and, it was added, as a footnote: "It is probable that exact electrical investigation, as well as Trousseau's symptom, would afford a means of recognizing a *latent condition of the disease, or that condition in which no attacks of tetany are present, though the disease is not entirely cured. The persistent increase of faradic, and especially of galvanic, excitability would constitute the characteristic symptoms of this condition.*" (The italics are mine.)

In the same paper it was observed that "the period of latency, in particular, may last for a long time, and apparent relapses are certainly often only indicative of the fact that the disease had not entirely run its course."

eight weeks of life, and that the values given by Thiemich and Mann for children over 8 weeks of age are too low for children between 8 weeks and 24 months of age. He gave as the values for normal children under two years of age:

C. C. C.	A. C. C.	A. O. C.	C. O. C.
3	>5	>5	>5
(exceptionally 1 to 5)	or <5		

No mention was made of the values for children over two years of age.

Thiemich had determined the values in cases of tetany in children under three years of age, and for these had given the formula:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
Tetany, manifest....	0.63	1.14	0.55	1.94

These figures were obtained by averaging the actual values found. They stand in sharp contrast with the normal values as given by Thiemich for children over 8 weeks of age, and in still greater contrast with the normal values given by von Pirquet for infants under 2 years of age.

The values found in Thiemich's cases of latent tetany in children were:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
Tetany, latent.....	0.70	1.45	0.95	2.93

Here, also, neither the highest nor the lowest values actually found are given, but only the average of them all. It will be noticed that Thiemich's phenomenon, or the occurrence of cathodal opening contractions under 5 ma., is present, and the anodal opening is lower than the anodal closing value, in the formulas both for latent and active tetany. Taken in all, the values of the formulas given by Thiemich for latent and active tetany are so nearly alike that we may regard the two formulas as practically the same. There is a very great difference between them and the normal and very little danger of confusion.

Von Pirquet's observations, however, made it apparent that in cases of latent tetany particularly figures not deviating so far from the normal are to be expected and, as outlined above, he identified anodal hyperexcitability with latent tetany, and cathodal excitability with active, manifest tetany. However, he stated distinctly that his observations were made upon infants.

Many writers have not hesitated to utilize the data obtained upon infants and young children and consider them applicable to older children. Yanase,²³ for example, working in Vienna, applied the formulas obtaining in infancy to children of 5 and even 8 years of age, and finding in them anodal, and occasionally cathodal, hyperexcitability,

23. Yanase: *Jahrb. f. Kinderh.*, 1908, lxvii, 57.

made diagnoses of tetany. Peritz²⁴ (1912) says specifically that Eschrich's value of 5 ma., for the anodal opening contraction as an expression of heightened excitability certainly applies to older children; and, further, that the early appearance of anodal opening contractions (that is, A. O. C. <5 ma.) seems pathognomonic of tetany in older children.

More recently Sedgwick²⁵ has examined the mothers of children that he thought spasmophilic and has been surprised at finding in the mothers values that compared with the formulas of infancy are abnormally low. Low values, as tested by the same standard, were found also in fathers and older brothers and sisters of such children. From these findings he has drawn far-reaching conclusions regarding spasmophilic families, in which the hereditary taint manifests itself in the children in the form of repeated absences or mild epileptiform attacks.

Now Stintzing has shown us that the value for the C. C. C. (cathodal closing contraction) for the peroneal nerve in adults ranges from 0.2 ma., which he calls the lower limiting value, to 2 ma., the higher limiting value. The Westphals, Mann and Thiemich, von Pirquet and others have shown that much higher values are to be expected in normal infants and, indeed, in children up to the third year. It is evident that a transition from the high normal values of infancy to the relatively low values of adult life occurs somewhere between the second year of life and puberty. When and how these changes occur has not been hitherto reported.

The recent clinical development of the conception of latent tetany forces this lack of knowledge upon our attention. The clinician who attempts to diagnose tetany or latent tetany in older children at once finds himself hampered by the inadequacy of published data regarding the course of galvanic excitability of the peripheral nerves in normal children. Ibrahim²⁶ has well said, in criticizing Sedgwick's paper on repeated absences, that it cannot be accepted as proved that the values that are pathognomonic for infants have the same diagnostic importance in older children and adults. Control examinations of normal children are very much to be desired.

It has seemed wise for these reasons to investigate the range of galvanic electrical values in a large number of children from birth up to thirteen years of age, and to record not only the average values, but also the highest and lowest values found in normal children of each year of life, together with any changes in the reactions that might be of importance.

24. Peritz: *Nervenkrankheiten*, Berlin, 1912, p. 444.

25. Sedgwick, Julius Parker: *Spasmophilia with Especial Reference to Familial Reactions and Repeated Absences*, *AM. JOUR. DIS. CHILD.*, 1914, vii, 140.

26. Ibrahim: *Ztschr. f. Kinderh.*, 1914, *Referate*, viii, 22.

The results of such an examination of a large number of average dispensary and hospital patients are herewith presented in tabular form.

The clinical material for examination was obtained from all patients admitted to the wards of the Harriet Lane Home from November, 1913, to April, 1914. These patients were tested as part of the first routine examination, and the test was repeated, as a rule, at intervals of a week or ten days thereafter during the patient's stay in the hospital. As many cases as time permitted were selected at random each day from the children in the outpatient department, and when a patient had been once tested an effort was made to repeat the test upon several subsequent visits. This practice applied also to former hospital patients.

Such patients are admittedly not normal children in the strictest sense of the word. The expression "normal children" is here used to designate those entirely free from evidences of clinical or latent tetany. Some of them were perfectly normal; some of them were brought for minor ailments, while others were suffering from, or convalescent from, severe illnesses. A few were epileptic or mentally retarded. There was no reason to suppose that any were not normal so far as their electrical reactions were concerned.

Four hundred and thirty-four patients were examined in all. Thirty-four of these were felt to be definitely abnormal, from the point of view of the study in hand, and were excluded from the present tabulation.

Of the thirty-four patients excluded from tabulation, thirteen were patients with latent or active tetany. The majority of them were admitted to the hospital for further study. In the other twenty-one cases the values obtained upon examination (first or subsequent) differed so widely from those of the ordinary child of the same age that it was thought best to exclude them from the series. Among them were three cases of hydrocephalus (with spasticity of the lower extremities) and other cases of abnormalities of the central nervous system, some of which will be discussed at the close of the paper.

The Technic of Examination.—With the child on his back, the examiner stood on the child's right and supporting the right knee and leg with his left hand, applied the stimulating electrode with his right hand.²⁷

An assistant, standing opposite the examiner and holding the indifferent electrode in place on the epigastrium with one hand, controlled the electrical apparatus with the other.

27. With the examiner standing in the position here described, slight movements of the foot, toes and tendons may be seen, and minimal contractions in the muscles of the lower leg may be felt, particularly in infants, by the fingers of the left hand as they rest on them. Voluntary movement of the leg is also restrained.

The apparatus was a silver chlorid battery of thirty-five cells, with the amperemeter in the direct circuit and reading fifths up to ten milliamperes.

The stimulating electrode consisted of a spherical metal ball of 1 cm. diameter mounted on a wooden handle bearing a make-and-break key, and the indifferent electrode of a metal disk 4 cm. in diameter. Both electrodes were covered with a thin layer of sponge to retain moisture and were moistened in warm water for use. In young infants the stimulating electrode was held firmly in the popliteal space—maximum contractions for minimal strength of current may be thus obtained in infants. In well-grown infants, and in children over 1 year of age, the point of maximum sensitiveness (Erb's point for the peroneal nerve) was sought, and being found, was retained throughout the examination.

The cathodal closing values were first sought by using a current sufficient to provoke a contraction. The strength of current was then diminished as rapidly as possible until contractions just ceased to appear. The reading at the appearance of minimal contractions, the needle always being allowed to come to rest, was recorded.

After waiting a few moments the anodal values were sought, beginning, as a rule, with about 5 ma. of current, diminishing it, and noting, as before, at what point minimal contractions appeared.

After again waiting, the cathodal opening value was similarly sought. The early appearance of cathodal closing tetanus sometimes prevents one obtaining a cathodal opening contraction; and in such cases cathodal closing tetanus alone was recorded.

The facial phenomenon (Chvostek), if present, was recorded in terms of its grade.²⁸

In no case was an anesthetic used and, save in two instances, it was never found impossible so to accustom the child to the procedure that a successful examination was possible. Infants were frequently examined while sleeping, without awakening them.

Rickets.—Tetany is no longer regarded as a symptom of rickets; but both are generally believed to be related in some way to disturbances in calcium metabolism. It is therefore necessary to review the conditions under which rickets appeared in the 400 children whose electrical values are here tabulated.

The number of cases (thirty-six) in which the presence of rickets was noted as other than the principal diagnosis—it was recorded as the principal diagnosis in seventeen cases—may appear small in comparison with the total number of cases tabulated (400); but this seeming disparity disappears when comparison is made with the number of individuals (100) examined between the sixth month and the third year, the period of active rickets. Then, too, the majority of cases of clinical tetany found during the period of study (see above) also presented signs of rickets, and the exclusion of these from the present table further reduces the percentage of rickets recorded therein. Possibly more cases suffered from rickets in some slight degree but not sufficiently to be clinically recognizable.

Examination of those individual cases in each age group which gave electrical values below the average for that group, showed that rickets was present with frequency only in Group 1 to 6 months and Group 1 to 2 years. In the former group it was present in 37 per cent. of the cases showing electrical values

28. Escherich records the Chvostek phenomenon in three grades, thus: Grade 1: Slight twitching at the angle of the mouth or of a small muscle bundle in the nose or forehead, following tapping with a percussion hammer or bent finger on a point midway between the pons zygomaticus and the angle of the mouth, over the facial plexus; Grade 2: A strong lightning-like twitch at the corner of the mouth, alae nasi, orbicularis, or frontalis muscles; Grade 3: A definite twitch in all the muscles supplied by the facial nerve upon tapping over it in front of the external auditory canal.

notably lower than the average. In the latter group it was present in 65 per cent. of the cases showing noticeably low values, and the lowest values included in the statistics for that group occurred in three cases of florid rickets.

In examining the tabulated results it is seen that the children are grouped according to age, and the number of children examined in each age group is given, together with the total number of examinations. The values obtained on galvanic electrical examination are presented

TABLE 1.—AVERAGE ELECTRICAL VALUES OF NORMAL CHILDREN OF DIFFERENT AGES

Age of Child, Years	Number of Children Examined	Average of Values Obtained in Normal Children				A. O. C. Less than A. C. C. %	Chvos-tek Phen., %	Total Number Examined
		C. C. C.	A. C. C.	A. O. C.	C. O. C.			
Under 1 mo.	29	>5	>5	>5	>5	0	..	39
1 to 6 mos.	56	3.9	4.9	>5	>5	8	0	157
½ to 1	38	3.3	4.7	4.6	>5	20	0	68
1 to 2	41	2.9	4.6	4.6	>5	36	0	78
2 to 3	20	2.5	4.2	4.3	>5	30	5	31
3 to 4	24	2.3	4.2	4.2	>5	40	0	42
4 to 5	20	2.1	3.8	4.1	>5	40	0	25
5 to 6	22	1.9	4.1	3.7	>5	67	14	43
6 to 7	20	1.8	3.9	3.0	4.9	75	5	36
7 to 8	20	1.9	3.7	3.2	4.9	65	5	22
8 to 9	30	1.7	3.9	3.5	>5	60	16	41
9 to 10	20	1.8	3.8	3.2	4.9	55	25	38
10 to 11	20	1.8	3.6	3.5	4.9	50	20	28
11 to 12	20	1.5	3.5	3.1	5.0	40	25	24
12 to 13	20	1.7	3.6	2.3	5.0	55	20	28

under three heads: (1) the average values;²⁹ (2) the highest values discovered, provided those did not exceed 5 ma.; and (3) the lowest values found in children who did not present other signs of latent

29. In computing the average values, values >5 ma. were treated as 5 ma, and the appearance of cathodal closing tetanus was regarded as the equivalent of a cathodal opening contraction of the same number of milliamperes; that is, C. C. Te=4.2 ma. was regarded as the equivalent of C. O. C.=4.2 ma. Now since A. C. C. >5, for example, may, in a given instance, stand for A. C. >6 or 8 or 10, it is clear that such a method of computing may give an unduly low average value, particularly in infants, in whom the A. O. C. and C. O. C. values often range far above 5 ma.; yet, since it is not desirable to test for contractions with current of greater strength than 5 ma., some such method of computing must be employed. In the data for older children this source of error is practically excluded, since in them the prevailing values are below 5 ma.

tetany. Under each group is indicated also the frequency with which there appeared anodal opening contraction with a current less than that causing anodal closing contractions, that is A. O. C. < A. C. C., the so-called anodal hyperexcitability of von Pirquet.³⁰ The number of cases in which a positive Chvostek phenomenon appeared is also noted.

These are the average electrical values of normal children, obtained and computed in the manner described. Stintzing has shown, however,

TABLE 2.—EXTREMES OF ELECTRICAL VALUES IN APPARENTLY NORMAL CHILDREN

Age, Years	Lowest Values Found in Apparently Normal Children				Highest Values			
	C. C. C.	A. C. C.	A. O. C.	C. O. C.	C. C. C.	A. C. C.	A. O. C.	C. O. C.
Under 1 mo.	3	4.2	>5	>5	>5	>5	>5	>5
1 to 6 mos.	1.6	3.4	>5	>5	>5	>5	>5	>5
½ to 1	1.9	2.0	2.9	>5	>5	>5	>5	>5
1 to 2	1.2	2.4	2.1	>5	>5	>5	>5	>5
2 to 3	1.2	2.8	2.5	>5	>5	>5	>5	>5
3 to 4	1.2	2.9	2.4	>5	4.5	>5	>5	>5
4 to 5	1.4	2.8	2.7	>5	2.9	>5	>5	>5
5 to 6	0.5	2.1	1.4	3.8	>5	>5	>5	>5
6 to 7	1.0	2.6	1.8	4.3	3.0	>5	>5	>5
7 to 8	1.1	2.2	1.7	4.9	2.8	>5	>5	>5
8 to 9	0.5	1.9	1.5	3.8	3.0	>5	>5	>5
9 to 10	1.1	2.7	2.1	4.7	3.0	5.0	>5	>5
10 to 11	1.1	2.0	2.0	4.7	3.0	>5	>5	>5
11 to 12	0.9	1.8	2.0	4.9	3.3	>5	>5	>5
12 to 13	0.3	1.8	1.5	>5	1.7	>5	>5	>5

how wide may be the range of electrical values in normal adults—the C. C. C. may be 0.2 to 2 ma. for the peroneal nerve at Erb's point, the average being 1 ma. There are analogous variations in infants and children. They may not be so great, but they exist.

There are presented here two other columns of figures, one showing the highest values discovered during the examination of the children in each age group, the other showing the lowest values found in children that were not subjects of active or latent tetany, so far as could be determined by careful examination, questioning, and by the observations of their subsequent symptoms.

30. See page 7.

It is difficult to know what interpretation to put on low electrical reactions in apparently normal children. There was sometimes found one figure, for example a C. C. C. value, which was very low, while all the other figures were high; but in general when one figure was high all were high, and vice versa. The low figures in Table 2 were found in individual patients, and are not compiled from isolated observations in several patients.

It can be understood that it is often exceedingly difficult to differentiate between the normal and the abnormal by electrical reactions alone, and it is frequently impossible to determine at the first examination whether younger children presenting low values are really suffering from a low-grade latent tetany. Later on, illustrative cases will be given, but the danger of including improper cases in the table of averages has led me to discard all those with unusual, isolated and unexplained low electrical values.

From these tables certain conclusions stand out clearly:

1. There is a gradual transition from the high electrical values of early infancy to the relatively low values of adult life.

2. Values below 5 ma., other than cathodal closing values, are rare in the first six months of life, but appear with increasing frequency thereafter.

3. Cathodal opening contractions with a current of less strength than 5 ma. are of infrequent appearance in normal children of any age; they probably do not occur in normal children under 5 years of age. The same may be said of cathodal closing tetanus. The occasional appearance of either after 5 years is not, per se, pathognomonic of tetany, but such children should be carefully examined for other evidences of tetany.

4. The presence of anodal opening contractions with a current less than that causing anodal closing contractions and under 5 ma. (anodal hyperexcitability) occurs with gradually increasing frequency from the first half-year of life upward, reaching its maximum frequency at 6 or 7 years. The infrequency of its occurrence in infants under 6 and 12 months of age (incidence 8 and 20 per cent., respectively) renders its appearance in them of considerable diagnostic importance, since this inversion of the usual sequence, as has been shown by others, may be, in cases of tetany, a forerunner of that cathodal hyperexcitability which usually accompanies manifest tetany. After the second or third year the presence of anodal opening contractions under 5 ma. in itself affords little help in diagnosis.

5. The facial phenomenon (Chvostek) is rarely met with in normal children under 5 years of age; it appears with increasing frequency thereafter.

6. There appears to be a rather abrupt transition toward adult values at the fifth to sixth year of life. In the age group 5 to 6 it is seen (a) that much lower values than hitherto were obtained in apparently normal cases; (b) that inversion of the earlier relation of anodal opening and anodal closing contractions appears in the formula of aver-

age values, and (c) that the facial phenomenon (Chvostek) appears with much increased frequency.

Knowing the galvanic electrical values that may be expected in normal children in each year of life, one can now proceed with some confidence to a critical examination of the electrical reactions that have been held by various authors to indicate the presence of tetany in infancy and childhood.

It should be emphasized that one low electrical value, no matter how low, is not in itself evidence of tetany. This is true especially of a low cathodal closing value. A low anodal value is of greater importance. If such appears to be present, the fact should be verified by a second examination a few minutes later. In clearly defined cases of tetany all values will, as a rule, be lower than usual.

In his earlier studies (1890 and 1897) Escherich stated that he found increased electrical excitability in all cases of tetany examined by him, and emphasized the early appearing cathodal closing tetanus as evidence of this. He considered hyperexcitability of the peripheral nerves the most important symptom of infantile tetany, which he defined as tetany occurring in children under 3 years of age, and said that at this age if electrical hyperexcitability were absent the diagnosis of infantile convulsions due to tetany could not be made, while certain conclusive conditions could only be recognized by its presence.

More precise statements were made by him in his monograph of 1909, or after the work of Thiemich and Mann, and von Pirquet. These will be considered later.

Escherich's earlier conclusions are sufficiently broad in their nature to admit of acceptance. Cathodal closing tetanus of anything more than the most momentary duration has not been found, in my study, in normal children under 5 years of age. The statement that electrical hyperexcitability is the most constant phenomenon in tetany of infancy has been generally accepted.³¹ The question is, what values exactly indicate the presence of abnormal hyperexcitability, that is, what figures indicate overstepping the limits of normal variation?

Thiemich and Mann, at the conclusion of their studies, declared that in cases of tetany the values for cathodal closing contractions are lower than in normal infants, that there is an almost uniform occurrence of anodal opening values less than anodal closing values ($A. O. C. < A. C. C.$), and that cathodal opening contractions ($C. O. C.$) appear under 5 ma. (Thiemich's phenomenon). This last phenomenon they considered characteristic of tetany.

31. This is not to imply that electrical excitability (electrical values) may not rarely be perfectly normal in cases of clinical tetany at the time of making any single observation (see page 18).

In considering Thiemich's views it is well to examine the actual figures given by him.³²

Thiemich and Mann's figures (averages) for cases of tetany are as follows:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
Tetany	0.63	1.14	0.55	1.94
Latent Tetany.....	0.73	1.45	0.95	2.93 ³³

Their averages for normal children under eight weeks of age are as follows:

C. C. C.	A. C. C.	A. O. C.	C. O. C.
2.61	2.92	5.12	9.28

Children over eight weeks of age:

C. C. C.	A. C. C.	A. O. C.	C. O. C.
1.41	2.24	3.63	8.22

It has been thought by some later workers that certain children who suffered from less marked and unrecognized tetany must have been included in Thiemich's series of normal children, with consequent reduction of the averages. This seems evident from my figures for normal children, in comparison with which it appears that Thiemich and Mann's figures for normal children under eight weeks of age represent better the lowest figures found in normal children one year of age, and the average figures given by them for normal children over eight weeks of age are nearly as low as the lowest figures that I have found in normal children under a year of age, and lower than my average figures under five years. Not only are the figures given by Thiemich and Mann for normal averages too low, but the most infrequent occurrence of A. O. C. < A. C. C. (30 per cent. in the third year) is not indicated.

The lowest values tabulated by me for normal children under three years of age are as follows:

C. C. C.	A. C. C.	A. O. C.	C. O. C.
1.20	2.80	2.50	> 5

The average values are much higher:

C. C. C.	A. C. C.	A. O. C.	C. O. C.
2.50	4.20	4.30	> 5

There is thus seen to be a wide difference between Thiemich's averages for active and for latent tetany and the lowest figures founded by me in normal children.

32. Due allowance should be made for the fact that Thiemich and Mann utilized the median nerve in their study. Later investigators have used the peroneal nerve (see page 6).

33. The figures for the two conditions are so nearly alike that they may practically be regarded as the same.

Though it is true that most cases of active, clinical tetany give findings that are much below the normal, and thus resemble Thiemich's findings more or less closely, yet there are other cases occasionally met with of undoubted clinical tetany which at no time in their course give findings as low as those of Thiemich and Mann for active and latent tetany.

If Thiemich and Mann's figures are made criteria of the presence of tetany, few erroneous diagnoses of tetany will be made, but many less-marked examples of clinical tetany will escape diagnosis, and most instances of latent tetany in which the electrical phenomena alone are present will pass unrecognized.

Von Pirquet stated his results very definitely and offered the conclusions given on page 7. He confined his study to infants, or children under two years of age. He divided them into three classes: (1) the normal; (2) those with latent tetany, and (3) those with manifest tetany. Those of the first class present only closing contractions under 5 ma.; those of the second class present anodal opening contractions under 5 ma.; while those of the third class (clinical tetany) give, in addition, cathodal opening contractions, or cathodal closing tetanus, under 5 ma.

Von Pirquet's conclusions are open to criticism. Anodal opening contractions under 5 ma. are frequently met with in infants under one year of age, and more frequently in children between one and two years of age. Anodal opening contractions under 5 ma. and under the value for the anodal closing contraction in the same patient, an even stricter definition of anodal hyperexcitability than is von Pirquet's, occur among normal children³⁴ with a frequency that increases progressively with the ages of the children until, in older children and in adults, it is a very common, if not regular, finding.

The phenomenon is met with in a considerable percentage of apparently normal infants under a year of age—probably about 10 per cent. It is not permissible, without further evidence, to say that such infants have latent tetany. They may show merely the early appearance of a phenomenon that is encountered with increasing frequency as age increases. The change is apparently one that accompanies normal growth, and one that finds several analogies, as, for example, the appearance of plantar flexion in response to plantar stimulation, a phenomenon seldom found in infants, more frequently met about the third year, and normally present in older children and adults.

Diagnostic significance would appear to be attached to the appearance of anodal hyperexcitability in infants, in children in whom it had not previously existed, or in connection with other suspicious condi-

34. See page 10 and Table 1.

tions. Its presence then becomes of diagnostic significance, and this significance is the greater the younger the child.

Escherich's later conclusions in his monograph, in 1909, were that there was as yet no general agreement as to the normal electrical values; that the values of von Pirquet were to be considered normal for the first year and indeed longer, though no exact studies for the later years of childhood had been made. Escherich accepted von Pirquet's three types of galvanic response in infancy, but questioned whether the milder grades of hyperirritability (von Pirquet's table) always indicate latent tetany.³⁵

With the publication of the tables in the first part of this paper, there are now available tables showing the electrical values found in normal children, tables that show both the average values and the extremes between which lie the actual values from which the average values are computed. The figures show that normal children present various degrees of galvanic electrical irritability. There is a wide normal variation that must be taken into account. The interpretation of electrical reactions must vary with the age of the subject examined. At no age is it possible to draw a sharp line between normal and abnormal reactions.

Certain broad statements, however, may be made for use in clinical work:

Electrical hypersensitiveness is the most common and constant phenomenon in tetany of infancy and childhood.

Whether tetany may exist without essential change in the electrical reactions of an infant or child cannot be dwelt upon here. Frankl-Hochwart and Chvostek are said to have noted such occurrences in the adult. Thiemich suggested such a possibility for the child. All the other phenomena of tetany have frequently been reported absent in individual cases of tetany. And we may ask, why not the electrical phenomena? Certainly, in their more marked grades they may be absent at the time of any given observation.³⁶ The essential relation between electrical hyperexcitability and the clinical manifestations of tetany cannot be said to be known. Nor can the cause of the frequent and sometimes daily variations (Case 8) in electrical hyperexcitability during the course of tetany be said to be known.

Cathodal opening contractions and cathodal opening tetanus, of anything more than momentary duration, with a current of less than 5 ma., do not occur among normal children under 5 years of age. If certain organic diseases, such as hydrocephalus, spastic paraplegia, and cerebral sclerosis can be excluded, the presence of C. O. C. < 5 ma. in

35. Escherich found a slight increase in electrical irritability in rachitis and organic nervous diseases, and Thiemich in microcephalus and cerebral sclerosis; in these cases the cathodal opening value lay above 5 ma.

36. See Case 8, January 5; Case 9; and Case 12, December 2 and 5.

children under 5 years indicates tetany. In children over 5 years, such is not necessarily the case.

The following cases show the value of C. O. C., and C. C. Te., < 5 ma. in diagnosis. One or two cases are also included to show that perfectly typical tetany may be present with the C. O. C. always greater than 5 ma.

CASE 1.—D. G., white girl, aged 8 months,³⁷ born in difficult, noninstrumental labor, was breast fed for three months, then given condensed milk mixture; during the last three weeks she was given cow's milk mixture, one half dilution. The child was born "blue" and remained so more than twenty-four hours. Jaundice appeared at birth and lasted six weeks. At the age of 5 months attacks "of getting blue and thumping of the heart" appeared. These came on without coughing, lasted five to ten minutes, and occurred three or four times a day at intervals of two or three days for one month. During the last two months the attacks were ushered in by sudden shortness of breath. First convulsion appeared eleven days before admission and lasted five minutes. The body became stiff, hands clenched and arms flexed; the tongue was bitten. Three similar attacks followed in the next three days, but were less severe.

The child was well developed and well nourished. There was slight epiphyseal enlargement. The spleen was not palpable. There was an inspiratory stridor. The thumbs were flexed on the palms, and there was a tendency to plantar flexion. The Trousseau phenomenon was present. The neck was rather short and thick. Roentgenography showed an enlargement of the heart and a probably enlarged thymus.

The child remained in the hospital twenty days and had no further convulsions until the last day. Her weight increased for ten days, then fluctuated, and during the last three days fell rapidly. The temperature at this time rose steadily from normal to 103.5. In the early morning the child was found hiccupping, cyanotic, and making convulsive movements of the tongue and facial muscles, with the respirations irregular. There was no obstruction to the passage of air. Chloroform inhalations relieved the convulsions. The abdomen was much distended. The rapid heart sounds became weaker and weaker, and the cyanosis increased until death occurred.

Electrical examinations in Case 1:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.		
Feb. 13.....	0.3	2.9	1.2	3.1	Ch. 1 ³⁸	Trousseau +
Feb. 15.....	0.9	1.9	1.4	3.9	Ch. 1	Trousseau +
Feb. 16.....	0.5	1.2	0.9	1.5	Ch. 1	
Feb. 17.....	0.7	2.6	1.2	3.8	Ch. 3	
Feb. 18.....	1.5	2.9	1.5	3.0	Ch. 3	
Feb. 20.....	0.9	2.7	1.3	3.2	Ch. 3	
Feb. 24.....	0.9	1.9	1.0	2.8		
Feb. 28.....	0.9	3.2	1.2	2.7	Ch. 2	
Mar. 3.....	1.4	3.5	1.8	4.8	Ch. 2	

A diagnosis was made of tetany, status lymphaticus, rachitis. The necropsy report showed general lymphatic hyperplasia, slightly enlarged thymus, cardiac hypertrophy and dilatation and a beginning bronchopneumonia.

This was a typical case of tetany. Even during the periods of freedom from attack there could be no question concerning the electrical values. They were much lower than the lowest values found in nor-

37. The age is always that at the time of making the first electrical examination.

38. Abbreviation for Chvostek, Grade 1, etc., see Footnote 28.

mal children of this age, and there was cathodal and anodal hyper-irritability, as well as the presence of the Trousseau and Chvostek phenomena.

CASE 2.—L. D. J., girl, age 8 months, of normal birth, was breast fed. During the first days of the patient's life the mother noticed that the child twitched and shook in her crib, and breathed noisily and with difficulty. Convulsions became more frequent and severe after the sixth month, and when received the patient was having from five to eight daily. During attacks, the child "got stiff," "worked" in the crib, twitched, breathed with difficulty, became dark around the mouth and eyes, and the anterior fontanel bulged. Attacks were said to last a half hour, after which the child fell asleep. The child was well nourished. The Chvostek phenomenon was negative, and no signs of rickets were present. The diagnosis was epilepsy.

Electrical examinations in Case 2:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
Mar. 26.....	3.2	4.4	3.7	> 5.0
May 2.....	3.6	5.0	4.4	> 5.0
June 25.....	4.0	> 5.0	> 5.0	> 5.0

This case stands in sharp contrast to Case 1. It seems clearly a case of epilepsy. The values obtained, while below the average for this age, are not lower than those frequently found in apparently normal children. All clinical signs of tetany were absent.

CASE 3.—G. W., colored boy, aged 20 months, of normal birth, was breast fed for fourteen months, with table food in addition. Five or six weeks before admission to the hospital, the child was croupy and had attacks of spasms. Croupy cough reappeared a week before admission, accompanied by spasms in which the child lost his breath and grew stiff for two minutes. These attacks occurred from twelve to fifteen times daily, more commonly at night, and were accompanied by carpopedal spasm.

The child was well developed and moderately well nourished. There was enlargement of the costochondral junctions and of the epiphyses. The spleen was not palpable. On the second day after admission the child had three general and severe convulsions, with several minor convulsions following during the night. Dyspnea developed, and laryngeal examination showed the epiglottis and cords greatly swollen and edematous. The child became cyanotic, but an intubation tube could not be passed, and tracheotomy was performed, with immediate relief. After tracheotomy the patient's temperature rose and remained elevated. Death followed an attack of dyspnea and cyanosis on the eighth day.

Electrical examinations in Case 3:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.	Ch. 2
March 19.....	0.9	2.1	2.0	3.5	

This case is one of severe tetany. The history is distinctive; the presence of a Chvostek phenomenon at this age almost always indicates tetany; and the electrical findings, especially C. O. C. < 5 ma., are conclusive.

CASE 4.—W. B., boy, white, aged 20 months, with past history not obtainable from the foster parents, five days before admission to the hospital was found "throwing himself about" and was cyanosed. He soon became stiff. The attack lasted in all about five minutes. Two similar attacks followed on succeeding days. They were preceded by a crowing sound, and always appeared when the

child was irritated. He seemed to bring them on by holding his breath. His thumbs were turned into his palms much of the time. He was a stout child with a short, thick neck. The superficial lymph glands were somewhat enlarged, and the tonsils were large. The spleen was palpable. The morning after admission, the child suddenly became cyanotic and dyspneic. This attack passed off, but a convulsion followed shortly with dyspnea, cyanosis and death, artificial respiration being unavailing.

Electrical examinations in Case 4:

C. C. C.	A. C. C.	A. O. C.	C. O. C.	Ch. 3
1.4	2.4	1.6	2.9	

The clinical diagnosis was tetany and status lymphaticus, with an anatomical diagnosis of status thymicolymphaticus, lymphoid hyperplasia, beginning rickets.

CASE 5.—A. L. S., girl, white, aged 7 years, breast fed until 9 months old, said to have had whooping cough at 4 years, moderately severe attack of measles six months before admission, and three attacks of tonsillitis in past, had always been well otherwise and had never had convulsions.

Following tonsillectomy under ether at 10 a. m., on September 26, the child complained of severe cramps in the feet and legs at 4 a. m., September 27. At this time her hands and feet were in the characteristic tetany position. Trousseau and Chvostek phenomena were present. As the result of sedatives and a hot bath, the child slept the greater part of the day, and in the late afternoon the cramps in the hands and feet had passed away, though the Trousseau and Chvostek phenomena remained present. Recovery was uncomplicated. There was no sign of rachitis.

Electrical examination in Case 5:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.	Ch. 3
September 27, p. m.	0.8	2.6	1.8	3.3	

Remarks: This child had been under the observation of Dr. Howland for six years. At no time previous to the above attack had she had any symptom suggestive of tetany. The attack came entirely unexpectedly, following a surgical operation. The child was seen in the following spring. At this time her reactions were as follows:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.	Ch. 2
March 21.	1.3	2.8	2.3	> 5.0	

She had no symptoms of tetany in the interim, and had been otherwise well.

The above case is an excellent example of clinical tetany following surgical manipulation of the neck in a 7-year-old girl. Its occurrence calls to mind all the theories of the Vienna school regarding the parathyroids and the supposed etiologic importance of disturbances of the blood supply due to prolonged assumption of unusual postures. The electrical values obtained, while typical of tetany at a younger age, were not lower than are found in some normal children of 7 years. Occurring in combination with undoubted clinical evidence of tetany, they scarcely admit of other interpretation.

CASE 6.—B. D., girl, colored, aged 2½ years, of normal birth, was breast fed for nine months, bottle fed for two months, then given table diet. After a normal infancy the patient suddenly developed carpedal spasm (May 10), and on the same day had a convulsion, falling down, becoming stiff, and frothing at the mouth. On the night before admission to the hospital, June 5,

contractures of the hands and feet were present for one and a half hours, reappearing the next morning.

The patient was a well-developed and moderately well-nourished child. Rickets was marked. There was a persistent carpopedal spasm. A bloody nasal discharge, with thick, mucopurulent secretion in the posterior rhinopharynx, was present. Throat culture was negative for *Bacillus diphtheriae*. The contractures of the hands disappeared on the second day after admission, and those of the feet on the third day. The Chvostek phenomenon had disappeared by the thirteenth day.

When seen again in November, the Chvostek phenomenon was elicited with difficulty, and the electrical reactions were not abnormal, but approached the lower limits of normal values.

Electrical reactions in Case 6:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
June 5.....	0.4	2.0	0.6	> 5
June 5.....	0.3	4.0	1.8	> 5
June 5.....	0.4	3.0	1.8	> 5
Nov. 21.....	2.0	2.9	2.4	> 5
Dec. 3.....	1.8	5.0	2.3	> 5

This case of clinical tetany in an older child (2½ years) shows that C. O. C. < 5 ma. is not necessarily present during the height of manifest tetany, a fact noted by Ganghofner in 1904.

The following cases are included to show that electrical reactions identical with those in tetany may be met in cases of hydrocephalus and spastic paraplegia.

CASE 7.—H. L., boy, white, aged 10 months, of normal birth, was breast fed for one month, then given proprietary foods and condensed milk and later cow's milk dilutions with sugar. At the age of 3 weeks the child suffered from a general convulsion, followed by stupor lasting for several hours. There had been no further convulsions, but at times the child had become rigid.

He was admitted to the hospital, April 18, as a poorly developed, poorly nourished infant, irritable, and somewhat spastic. The cranium was relatively enlarged and asymmetrical and the face small. There was fine nystagmus and a mild degree of choked disk. The reflexes were increased. The child was unable to sit alone and there was a rachitic rosary. The von Pirquet and Wassermann reactions were negative. There was little change in condition for one week; then there was rapid gain in weight (2 pounds, 12 ounces), and he was discharged May 28. He was treated thereafter in the outpatient department and did well.

Electrical examinations in Case 7:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.	C. C. Te.
April 25.....	0.9	3.2	1.9	4.0
May 22.....	3.1	> 5.0	4.1	> 5.0	
June	3.1	> 5.0	4.0	> 5.0	

In this case the Chvostek phenomenon was negative. A diagnosis of malnutrition and hydrocephalus was made. There was marked electrical excitability, without any other evidence of tetany, but with hydrocephalus.

Von Ranke³⁹ in 1894 noted the clinical resemblance to tetany⁴⁰ of early cases of hydrocephalus, with spasticity. The presence of cranial

39. Von Ranke: Zur Diagnose d. chronischen Hydrocephalus in dessen Anfangstadien bei noch nicht vorhandener Vergrosserung des Schädels, Wiener Naturforscher-Versammlung. Sept. 26, 1894, cited from Kalischer, Footnote 14.

40. See historical sketch, J. Cheyne, in early part of this paper.

enlargement, nystagmus and choked disk, and the absence of the usual clinical signs of tetany, are to be noted here.

CASE 8.—B. C., girl, white, aged $3\frac{1}{2}$ years, of normal birth, was breast fed for nine months, then weaned, and carefully fed thereafter. Slight convulsive movements had occurred before the child was 9 months of age, then numerous convulsions, until the time of admission. There had gradually developed paralysis on the right side, and eventually on the left side, with progressive mental and physical deterioration and spasticity of the extremities, but with no adductor spasm. There was slight Chvostek phenomenon.

After admission to the hospital, December 29, there were numerous clonic convulsions, sometimes ushered in by a cry, and there was marked rigidity. Rickets was not present. The von Pirquet was negative, Wassermann positive in both blood and spinal fluid. The child improved somewhat, and then declined, under vigorous antisypilitic treatment. She was discharged unimproved.

Electrical examinations in Case 8:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.	C. C. Te.
Dec. 31 (right).....	1.9	1.9	2.0	> 5.0	
Dec. 31 (left).....	1.9	2.9	2.5	> 5.0	
Jan. 5.....	1.7	1.9	> 5.0	> 5.0	
Jan. 12.....	0.7	2.9	3.6	4.0 +
Jan. 21.....	3.1	> 5.0	> 5.0	> 5.0	
Jan. 24.....	2.0	4.0	> 5.0	> 5.0	
Jan. 29.....	1.9	2.9	1.0	> 5.0	
Feb. 9.....	2.2	3.0	> 5.0	> 5.0	
Feb. 18.....	1.5	1.9	1.7	4.0

This is an example of typical electrical reactions of tetany, appearing in a case of spastic paraplegia due to hereditary syphilis.

Anodal opening contractions appearing with a current less than that causing anodal closing contractions, and less than 5 ma., during the first six months of life are pathognomonic of tetany in almost all cases; their appearance with a current less than 2 ma. is probably pathognomonic of tetany up to the fourth or fifth year; thereafter their appearance alone is of little significance.

With anodal hyperexcitability we are undoubtedly dealing with a lower grade of excitability than with cathodal and with one which is rather indefinitely separated from the normal. This follows from the wide range of galvanic excitability found in normal children. The range of normal variation appears to become greater as children increase in age, and therefore the difficulty of determining abnormal degrees of excitability is increased in older children.

In practice the difficulty is not so great as it might seem. The majority of cases of clinical tetany present values that are evidently far below the normal (for example, Cases 1 and 4). Furthermore, the great majority of cases of true clinical tetany in childhood occur during infancy, the period when the difficulty of electrical diagnosis is slightest.

As a rule the electrical diagnosis of tetany can be readily made, provided the child be examined early enough and frequently enough. By

frequently enough is meant daily examination for a short period. Cases 9 to 12 serve to illustrate these points.

CASE 9.—A. M., boy, white, aged 5 months, of normal birth, was breast fed for two months and then given cow's milk and various infant foods. He was poorly nourished. There were no symptoms of tetany. He was admitted to the hospital September 27, and gained weight satisfactorily. He was treated in the outpatient department after December 5, and did well.

Electrical examinations in Case 9:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.	C. C. Te.
Oct. 22.....	4.8	> 5.0	> 5.0	> 5.0	
Nov. 4.....	3.0	3.8	5.0	> 5.0	
Jan. 26.....	2.7	> 5.0	3.0	> 5.0	
Jan. 29.....	1.5	2.4	1.9	4.3
Feb. 10.....	0.7	3.0	1.9	4.0 +
Feb. 27.....	1.4	3.0	1.8	3.5	
Mar. 12.....	2.9	> 5.0	3.0	> 5.0	
April 6.....	4.5	> 5.0	> 5.0	> 5.0	
May 18.....	3.1	> 5.0	> 5.0	> 5.0	

The Chvostek phenomenon was doubtful, and there was no evidence of rickets found. The patient was an artificially fed infant in whom electrical hyperexcitability developed while under observation.

The case is to be regarded one of latent tetany in which recovery took place without developing symptoms of manifest, or clinical, tetany. The appearance of anodal hyperexcitability (January 26) in an infant of 7 months in whom this had not previously existed was the first evidence of the presence of heightened excitability of the nervous system. This was followed quickly (January 29) by cathodal hyperexcitability and the condition of increased excitability persisted for a month, and then disappeared without the development of any symptoms.

CASE 10.—R. B. A., boy, colored, aged 5 months, breast fed, with supplementary feedings later, was a healthy infant, well nourished, with no symptoms of tetany, but with beginning rickets.

Electrical examinations in Case 10:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
Oct. 25.....	2.0	5.8	3.0	> 5.0
Nov. 6.....	2.0	3.8	2.7	> 5.0
Nov. 18.....	2.2	> 5.0	> 5.0	> 5.0
Dec. 3.....	2.2	> 5.0	2.4	> 5.0
Dec. 26 (right).....	2.0	4.5	2.8	> 5.0
Dec. 26 (left).....	2.1	4.3	3.0	> 5.0
Dec. 30 (right).....	1.0	3.1	1.2	4.7
Dec. 30 (left).....	1.2	2.5	1.4	4.8
Jan. 3.....	2.8	3.1	3.1	> 5.0
Jan. 12.....	2.7	4.0	2.9	> 5.0
Jan. 21.....	3.1	3.9	3.9	> 5.0
Jan. 30.....	2.7	> 5.0	3.5	> 5.0
Feb. 7.....	2.1	> 5.0	3.0	> 5.0
Mar. 26.....	1.7	2.4	2.4	> 5.0
May 15.....	1.7	3.0	3.0	> 5.0

The Chvostek phenomenon was positive after the eighth month. The diagnosis of latent tetany is justified by the presence of anodal and cathodal hyperexcitability and a Chvostek phenomenon of moderate grade in a child with rickets.

Children suspected of tetany should be examined a number of times. Variations in electrical excitability are common during the course of the disease. In the above case the evidence of increased excitability was discovered during a routine examination (October 25), persisted for a time, and then disappeared entirely (November 18), only to return in more marked degree during the succeeding weeks.

CASE 11.—D. B., girl, colored, aged 18 months, of noninstrumental birth, but infant blue and respiration established with great difficulty, was breast fed for nine months, then given condensed milk and cereal. On January 10 the mother noticed that the child could no longer stand up when placed on her feet and that the feet and legs were swollen. There was fever. These symptoms continued until admission to the hospital. The child cried out in pain at times and drew her feet up. The swelling of the feet increased and the hands became clenched. Convulsive attacks appeared with increasing frequency.

She was a well-nourished child, with distinct evidences of rickets. There was slight bowing of the tibiae and lateral retraction of the chest wall. A condition of situs inversus of the viscera existed, but there was no general glandular enlargement. The spleen was just palpable. The Chvostek phenomenon was very marked, the very slightest touch producing marked contraction of the facial muscles. Typical carpopedal spasm existed. The child was admitted to the hospital February 2. The condition improved slowly, with no convulsions and no carpopedal spasm after February 5. Trousseau's sign was present until February 14. Chvostek phenomenon was less active after this date, but still marked.

Electrical examinations in Case 11:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
Feb. 2.....	1.2	3.0	1.8	7.5 (5.2)
Feb. 3.....	0.4	3.0	1.1	2.1
Feb. 5.....	0.8	2.2	1.6	4.0
Feb. 9.....	0.8	2.2	1.4	4.0
Feb. 13.....	1.5	2.0	2.0	3.0
Feb. 20.....	2.1	2.4	2.3	4.5
Feb. 18.....	1.8	3.0	3.5	5.0
Feb. 26.....	2.0	3.0	3.5	? (near 4.5)

The rapid appearance of cathodal opening values below 5 ma. is here interesting. It was preceded by marked symptoms and signs of tetany and by anodal hyperexcitability (February 2) which in this case was but little more marked than that found in a few apparently normal children (see Table 2). The appearance of cathodal hyperexcitability next day (February 3) was coincident with the cessation of convulsions.

CASE 12.—J. W., boy, colored, aged 11½ months, of full-term, noninstrumental birth, no cyanosis at birth, was breast fed for ten months, then given supplementary feedings of cow's milk. There was an indefinite history of convulsive attacks when the child was 9 days old, but otherwise he was apparently healthy. At four months he had whooping-cough with "nervous twitchings" of the hands. On the night of December 1 the child (then 11 months old) was feverish, restless and breathed very loudly, but there was no cough. Early next morning the child had a convulsion. In the afternoon the child had another convulsion, lasting three minutes.

He was a well-nourished child, temperature 102, throat slightly injected, with adenoids and a marked high-pitched inspiratory stridor. There were marked rachitic rosary and Harrison's grooves, and superficial glandular enlargement. The abdomen was slightly distended, spleen not palpable, reflexes difficult to obtain. No spasticity or paralysis was present. Chvostek and Trousseau phenomena were present.

Electrical examinations in Case 12:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.	
Dec. 2 (right) ...	2.4	4.5	3.5	>5	Ch. +
Dec. 2 (left)	2.8	4.8	3.8	>5	
Dec. 3 (right) ...	3.5	>5	>5	>5	
Dec. 3 (left)	3.7	>5	4.7	>5	Ch. 0
Dec. 4	Ch. +; Trousseau, suggestive
Dec. 5, 12 m.	3.4	>5	>5	>5	Ch. very faint
Dec. 5, 2 p. m.	2.4	>5	2.1	>5	
Dec. 7	2.0	3.5	2.2	>5	Ch. +; Trousseau +
Dec. 7 (later) ...	3.2	>5	3.1	>5	Ch. +

During the next four weeks there were no signs of tetany, with Chvostek doubtful:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
Jan. 14	>5	>5	>5	>5

There was striking daily variation of signs during the course of the tetany.

The case is of importance in showing the undoubted occurrence of normal electrical values during the course of tetany in infancy. The period of apparently normal electrical values was preceded by one of low electrical values, and followed by yet lower values. The presence at various times of all the other characteristic signs of tetany established the diagnosis. A single examination in this case, for instance, on December 3, might have led to an entirely erroneous diagnosis if the electrical examinations alone had been considered.

Tetany in Older Children.—By the term "older children" is here meant children of more than 3, and, more especially, of more than 5 years of age. In them the electrical diagnosis of tetany becomes difficult. The electrical standards of infancy certainly do not apply to older children. Formulas that in the infant would indicate the presence of tetany are common in healthy and apparently normal older children. Anodal hyperexcitability in its strictest definition becomes a frequent occurrence about the third year (40 per cent. in our series—see Table 1), and after the fifth year becomes the prevailing condition (67 per cent., in the fifth year, and 75 per cent. in the sixth year). Some children preserve the infantile formula as late as puberty, and physiologists differ as to which condition prevails in adult life. The occurrence of cathodal hyperexcitability (Thiemich's phenomenon) is not unusual in normal children over 5 years of age. The Chvostek phenomenon occurs frequently and in its lower grades (see Footnote 28) appears to be generally without significance.

The standards that have proved useful in infancy become less serviceable with increasing age. In children over 5 years of age it is necessary in making a diagnosis of tetany to adhere more closely to the criteria generally accepted for the diagnosis of tetany in adults.⁴¹

The electrical diagnosis of tetany, or even latent tetany, in older children by the standards of infancy rests on the most insecure foundation. Cases 13 and 14 will serve to illustrate the correctness of these statements.

CASE 13.—E. McK., boy, white, aged 8 years, of instrumental birth, was reared on diet poorly chosen, but not unusual. There were no symptoms of tetany. There was complaint of the presence of tapeworm. The child had never had convulsions, but there was a history of pertussis (1909), chicken-pox (1911), measles (1913), of an operation for abscess of neck (1910), and of otitis following measles. The present trouble began in 1911, and the child was treated with anthelmintics on two or more occasions. He was admitted to the hospital for three days, November 10. After treatment the patient passed seven feet of *Taenia saginata* segments. The Wassermann test, which was made because of suggestive family history and enlarged spleen and epitrochlear glands, was markedly positive. Antisyphilitic treatment was begun, and the child did well. He was readmitted to the hospital on January 28 because of the appearance of segments in the stools, and after treatment he passed six feet of worm.

Electrical examinations in Case 13:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
Nov. 10.....	0.3	1.4	1.2	2.4
Nov. 13.....	1.0	2.2	1.9	4.2
Jan. 28.....	0.25	2.1	1.9	4.8

The Chvostek phenomenon was not present at any time and no evidence of rickets was found.

This case is mentioned because of the extremely low electrical values found during the course of a routine examination. The patient was without suggestive history or symptoms. The reason for the occurrence of such low values in this child is not known. He was excluded from the series of normal reactions.

CASE 14.—A. R., girl, white, aged 9 years, with a mentally deficient Jewess as a mother, with a noninstrumental, but prolonged and difficult birth, was breast fed for eighteen months. The child is said to have suffered from "spasms" (abdominal cramps?) until 1 year old, but to have had none thereafter. She was brought to the outpatient department for treatment because of hyperesthesia and fleeting body pains that were occasionally sharp. She was poorly nourished and habitually constipated. The treatment from November 6 to February 14 consisted of tonics, better hygiene, half-time schooling, and correction of an error of refraction. The child improved steadily in appearance and her complaints became fewer, though there were occasional bad days.

On February 14 she was admitted to the hospital for closer observation, with complaint of pain in the right axilla, over the thorax, and around the heart. Examination showed normal temperature and pulse, carious teeth, palpable left thyroid lobe and exaggerated reflexes. The von Pirquet test was positive. The patient was discharged after five days, nothing further of importance having been found.

41. See standard texts, such as Oppenheim's Lehrbuch.

Electrical examinations in Case 14:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.	C. C. Te.
Nov. 6.....	<0.3	1.8	1.7	4.5	5.2
Nov. 8.....	0.6	2.1	1.5	3.2	3.5—4.5
Nov. 15.....	0.8	4.4	2.0	>5.0	
Nov. 20.....	0.9	3.0	1.9	4.4	
Dec. 2.....	1.1	4.2	2.0	>5.0	
Jan. 17.....	0.7	2.7	1.6	5.0—	5.0
Feb. 18.....	1.0	2.9	2.1	4.7	

The Chvostek phenomenon was present, but not marked. Rachitis was not present. The diagnosis was neuropathic constitution.

It is not easy properly to classify this case. Many authors have enumerated such complaints as those described as symptoms of latent tetany, or, more commonly, of the so-called spasmophilic diathesis. At first glance it might be thought that electrical findings like the foregoing support such a hypothesis, but closer examination renders this at least doubtful. The electrical values found in this patient are low, but they are not lower than those found in many children of her age (see Tables 1 and 2—seventy children between 8 and 11 years of age). The Chvostek phenomenon, also, occurs not infrequently in children of this age (25 per cent.; see Table 1). Vague complaints like those enumerated are not uncommon among children of the patient's race and generally disappear with improved environment. They are probably not due to latent tetany.

Escherich's views regarding the electrical findings in puerile tetany may here be mentioned. He defined puerile tetany as tetany occurring in children over 3 years of age. His views may be summarized as follows:

The recognition of latent symptoms is determinative, their value with certain limitations, being the same as in infantile tetany. Presence of the Chvostek phenomenon, if in high grade (Grade 3), is probably pathognomonic, and the Trousseau phenomenon is unqualifiedly pathognomonic, if hysteria is excluded. Studies in the electrical values are lacking (1906) for this age, and the normal values have not been ascertained. It may be assumed, however, that the high values of infancy gradually approach the Stintzing values for adult life; and that the C. C. C. lies within from 1 to 1.5 ma., while the other values are higher. That outspoken electrical hyperexcitability will express itself in the C. C. C. sinking to 1 or less than 1 ma., the appearance of opening contractions under 5 ma., and the early appearance of tetanus, especially C. C. Te.

Some doubt was expressed whether the electrical signs alone will suffice for the diagnosis at this age of tetany and tetanoid conditions. Actual observations in cases of puerile tetany, as cited by him are as follows:

	C. C. C.	A. C. C.	A. O. C.	C. O. C.
At 7 years.....	0.4	0.8	0.6	0.8
	0.8	2.8	2.8	2.4
	0.1	1.4	1.4	<5
	1.0	2.0	1.0	<5
At 13 years.....	0.5	3.0	1.0	3.0

Also at 10 years C. C. Te. at 2.0 ma., and at 7 years A. O. Te. at 4 ma.

It is not felt that a diagnosis of tetany or latent tetany is warranted in either of the last two cases.

CONCLUSIONS TO CLINICAL PART

1. The appearance of cathodal opening contractions under 5 ma. (and in the absence of certain conditions already mentioned) in children under 5 years of age is pathognomonic of tetany. Cathodal opening contractions are, however, not infrequently absent in cases of clinical tetany.

2. The appearance of anodal opening contractions with less current than that causing anodal closing contractions, and under 5 ma. during the first 6 months of life is probably pathognomonic of tetany in all cases; their appearance with less current than that causing anodal closing contractions and under 2 ma. is probably pathognomonic up to the fourth or fifth year; thereafter it is of little significance.

3. The appearance of a Chvostek phenomenon under 2 years, in the absence of birth trauma, indicates tetany; under 4 or 5 years of age it is highly suggestive of tetany; its appearance in the highest grade (Grade 3, Escherich) is suggestive throughout childhood. After 3 years the Chvostek phenomenon is not infrequently found in milder grades in apparently normal children.

4. The occurrence of any one of these symptoms in association with a clinical history of tetany is to be considered conclusive evidence of tetany.

5. The determination of the electrical values is an extremely useful, but not always an infallible, means of diagnosing active or latent tetany in childhood. It is most useful in infancy. Like other clinical tests, this one has definite limitations that must be recognized.

ELECTROCARDIOGRAPHIC STUDIES OF CONGENITAL HEART DISEASE *

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Congenital lesions of the heart may be divided into three groups, which are more or less independent of each other. These groups are anomalies of position of the heart, lesions of the structures controlling rhythm and conduction, and malformations of the chambers or orifices of the heart. The purpose of this paper is to report a group of cases in which the diagnosis of congenital heart disease has been made, presenting the electrocardiograms that have been obtained from them, and to offer an explanation for the form of electrocardiographic curve that has been associated with congenital heart disease. These cases have been under observation either in the St. Louis Children's Hospital or in the Washington University Dispensary during the past year. The electrocardiograms have been made at the Heart Station of the Department of Internal Medicine, under the direction of Dr. G. Canby Robinson.

Electrocardiograms that show a distinct difference from normal curves have been obtained by previous observers from cases of malformation of the heart, and it has been asserted that whenever electrocardiograms have been made from congenital malformations they have shown this variation from the normal. Such a point, if true, would be of great value in the diagnosis of malformations of the heart, especially if the curve is of a specific form, associated with no other condition. But before coming to such a conclusion it must be shown that such variations from the normal are constantly associated with lesions in a large number of cases, and it must be shown just what phenomenon in the heart is the cause of the abnormal form.

Einthoven¹ first called attention to an abnormal ventricular complex in congenital heart disease, but Steriopulo² first observed the form of curve that is usually associated with this condition. His curves were made from two cases and showed in Lead I, instead of the customary R wave of medium height and an S wave that is relatively small, a deep S wave and a very small R wave. He concludes that if these peculiari-

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1. Einthoven: *Arch. f. d. ges. Physiol.*, 1908, cxxii, 517.

2. Steriopulo: *Ztschr. f. exper. Path. u. Therap.*, 1910, vii, 467.

ties should show themselves to be characteristic in further examinations, then this method (electrocardiography) would play a great rôle in fixing the diagnosis of congenital heart disease. He also pointed out that great care must be exercised in the application of these findings, because it is not clear why this form of heart failure should show such unusual electrocardiograms. These observations were confirmed by Ratner,³ who studied seventeen cases of congenital heart disease under the direction of Nicolai. From these studies Nicolai concludes that the deep S wave in Lead I is a characteristic sign of congenital malformation of the heart, and he states he had never seen a case of congenital malformation that failed to produce a curve of this type. Hecht⁴ reports a series of nine cases, in two of which the S wave was absent in Lead I, and in one of these cases there was an unusually large Q wave. In the other seven cases the S wave was outspokenly prominent in one case, being much more so than the R wave. Einthoven⁵ notes that in several cases showing tricuspid insufficiency, high-grade mitral stenoses or changes of position, a negative electrocardiogram was constantly associated with a hypertrophy of the right chamber. These conclusions were borne out by observations on a case showing defects of the interventricular septum and patent foramen ovale. Lewis⁶ examined a series of twelve cases of congenital malformation of the heart in which cardiac enlargement, cyanosis and harsh systolic thrills and murmurs, maximal over the pulmonary cartilage, were the chief diagnostic signs. With two exceptions the electrocardiograms of these cases indicated generally extreme degrees of right-side hypertrophy. He further notes that curves showing signs of right-side hypertrophy with extreme amplitude of excursion are obtained only when there is reason to believe that congenital malformation is present; he says that exaggerated amplitude in several leads in itself is a valuable sign of congenital valve or septal defects.

In a paper such as this, it is not proposed to enter into a discussion concerning the influence that hypertrophy of the different chambers of the heart may have on the form of the electrocardiogram. Einthoven concluded from his studies that ventricular preponderance of one side of the heart or the other produces a very characteristic change in the electrocardiogram. The changes from the normal which he observed were that in right ventricular hypertrophy the S wave in Lead I is extraordinarily deep, and in Lead III the R wave is extraordinarily high. In left ventricular hypertrophy the R wave in Lead I is increased and in Lead III the S wave is increased. These observations

3. Ratner: Inaugural Dissert., Berlin, 1912.

4. Hecht: *Ergebnisse d. inn. Med. u. Kinderh.*, 1913, xi, 340.

5. Einthoven: *Zentralbl. f. Herz- u. Gefasskr.*, 1915, vii, 101.

6. Lewis: *Clinical Electrocardiography*, 1913.

have been further substantiated by other writers, notably by Lewis,⁷ in many conditions that cause a hypertrophy of the chambers of the heart. It can be said that the relation between the height of the different waves of the electrocardiogram and hypertrophy of the heart is not a settled question, yet there are many observations that tend to confirm Einthoven's original conclusions.

Newborn infants and those during the first six months of life have been shown to give electrocardiograms with a deep S wave in Lead I. Hecht⁴ and Lewis⁶ have observed babies at intervals during the first year of life and have recorded a decrease in the size of the S wave in the electrocardiograms as the children grew older. In infants who fail to develop normally the infantile type of curve may persist longer than during the first year of life. In explanation of these curves it must be remembered that as a result of the activity of the heart during fetal life, the right ventricle shows a relative hypertrophy, which disappears as the circulation in the heart and the normal relations of right and left ventricular activity become established. These observations also bear out Einthoven's ideas concerning the relation between ventricular hypertrophy and the height of the waves in the electrocardiograms.

The following group of twelve cases of congenital malformation of the heart, from which electrocardiograms were obtained, are confirmatory of the relation between right ventricular preponderance and the type of curve mentioned by Einthoven, in which there is a small R wave and a deep S wave in Lead I and a large R wave and a small S wave in Lead III. They also show that this type of curve is not diagnostic of a congenital malformation, as has been supposed, and that all congenital malformations do not show this type of electrocardiogram. That is, if the congenital malformation is of such a nature that a right ventricular hypertrophy results, one will obtain this type of a curve. If the malformation is not associated with this secondary hypertrophy, this type of electrocardiogram fails.

CASE 1 (Children's Hospital No. 8253).—W. M., aged 23 months, was admitted to the hospital with diagnosis of congenital malformation of the heart, with defect of the auricular septum. The heart condition was first recognized on admission to the hospital March 31, 1915. There was no cyanosis. A rather diffuse faint thrill could be detected, best felt in the fourth interspace, 2 cm. to the left of the midsternal line. A very loud, rough systolic murmur all over chest was perceptible, best heard in the third left interspace. The heart dulness extended 3 cm. to the right and 7 cm. to the left of the midsternal line, a distinct enlargement in both directions. The liver was 2 cm. below the costal margin, and the spleen could just be felt. Roentgen-ray examination showed the heart greatly enlarged to the right and the left, with a body length of 59 cm. The patient's weight on admission was 3,000 gm., and during the subse-

7. Lewis: *Heart*, 1914, v, 367.

quent year there was a very slow gain, but with many fluctuations, to 3,600 gm. at death, Feb. 7, 1916. The red blood cell count was 4,672,000.

Electrocardiograms (275, Fig. 1) were made Dec. 10, 1915. They showed a rate of 131.6 per minute; conduction time Lead II, 0.121 second, with mechanism normal.

STRENGTH OF CURRENTS IN CASE 1

	Millivolts
Lead I	R wave = 0.77
	S wave = 1.35
Lead II	R wave = 0.75
	S wave = 0.82
Lead III	R wave = 1.52
	S wave = nil

Necropsy (No. 601) was performed by Professor Opie. His diagnosis was congenital anomaly of the heart, defect of auricular septum, chronic endocarditis of pulmonary, mitral and tricuspid valves (?). The necropsy findings are as follows:

The heart weighs 35 gm. The right auricle is of large size. The anterior surface of the heart is formed in large part by the right ventricle, which is considerably larger than the left. On exposing the auricles a wide circular foramen, 1 cm. in diameter, occupies the position of the foramen ovale and

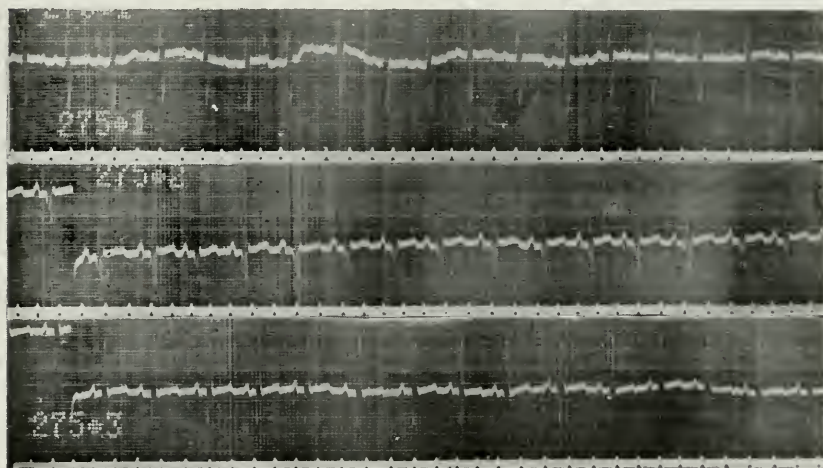


Fig. 1 (Case 1).—Defect of auricular septum; deep S wave in Lead I, high R wave in Lead III; right ventricular hypertrophy.

In this and the following illustrations the records were made directly on photographic paper. The tension of the string of the galvanometer was so adjusted that when 2 millivolts were thrown into the circuit, there was a deflection of the shadow of the string on the paper of 2 cm. Using this standardization, it has been possible to express the amplitude of the waves in terms of millivolts. In one instance (curve 350, Lead III, Fig. 8) the deflection was only 1 cm. for 2 millivolts. The time marker indicates fifths of a second. In measuring the amplitude of the waves and the conduction time at least ten heart cycles have been utilized in each estimation, the figures recorded being the average.

is wholly enclosed by a valvular fold. There is about the orifice a fairly narrow rim of tissue representing the interauricular septum. The right ventricle measures 3 mm. in thickness and is firm in consistency. The left ventricle measures 6 mm. The aortic valve is delicate and appears normal. Along the free edge of the mitral valve are translucent elevations which have the appearance of vegetations. There is a similar thickening along the free edge of the tricuspid valve. The free edges of the segments of the pulmonary valve are thickened and rounded, but otherwise there is no abnormality.

COMMENT

The clinical diagnosis presented no special difficulty, the only point being that it was not certain whether it was the auricular or ventricular septum that was patent, most of the evidence being in favor of the former. The electrocardiograms (Fig. 1) indicate a right ventricular hypertrophy. It was noticeable not only that there was a failure to gain weight normally on various foods, but also that there was no increase in body length and the child was backward in every other development. It is a very well known fact that congenital heart disease occasionally retards body growth and development very much and this patient is a striking example. It is probably of importance in this connection that there had not been any cyanosis.

CASE 2 (Children's Hospital No. 9738).—H. H., boy, aged 3 months, was received Jan. 20, 1916, with clinical diagnosis of congenital malformation of the heart, pulmonary stenosis (?), defect of interauricular or ventricular septum, and congenital syphilis.

Three weeks before admission there had occurred a spasm, during which the patient became blue. A much less severe spasm occurred ten days and a third four days previous to admission. These had been of very short duration, but the child had been blue each time and dark colored all the time. When the patient was seen in the hospital it was noted that there was irregular respirations suggesting Cheyne-Stokes type, associated at times with convulsive seizures of short duration, during which he became very cyanotic, especially about the face and head. At all times there was present a distinct duskiness of the skin, with definite cyanosis about the lips and buccal mucous membranes. There was slight clubbing of the finger tips. No thrills could be felt over the heart area. The point of maximum impulse was 2 cm. outside the nipple line. Dulness extended 1 cm. to the right and 6 cm. to the left of the midsternal line. There was a blowing systolic murmur, not very loud, heard at the apex, transmitted to the axilla and to the base of the heart. The murmur was faint but persisted. The second pulmonic tone was accentuated. The liver was 2 cm. below the costal margin. Roentgen-ray examination showed a broad heart shadow, with enlargement to the right and on the left, extending into the axilla. The Wassermann reaction was positive. Red blood cell count showed 3,968,000.

Electrocardiograms (332, Fig. 2) were made Jan. 21, 1916. They showed a rate of 126.4 per minute; conduction time Lead II, 0.121 second, with mechanism normal in Leads I and II. In Lead III the T wave was negative and there was considerable variation from the normal in the auricular complex, suggesting a diphasic action current.

STRENGTH OF CURRENTS IN CASE 2

	Millivolts
Lead I	R wave = 1.52
	S wave = 0.40
Lead II	R wave = 2.25
	S wave = 0.52
Lead III	R wave = 0.80
	S wave = nil

Necropsy (No. 596) was performed by Professor Opie. His diagnosis was congenital anomaly of the heart, fibroid atrophy of the right ventricle, hypertrophy and dilatation of the right auricle, patent foramen ovale, hypertrophy of the left ventricle. The necropsy findings are as follows:

The body length is 52.5 cm., weight 2,915 gm. The pericardium is of very great size, measuring 7.3 cm. transversely and 6 cm. from above downward. The pericardium contains a small excess of clear yellow fluid. The heart weighs 36.5 gm. When exposed, the right auricle is found to be of great size, forming only slightly less than one half of the anterior aspect of the heart. The right ventricle is of small size; the anterior surface of the left ventricle is about three times as great as that of the right. The right ventricle does not approach within 1 cm. of the apex. The left auricle is not distended. On section the cavity of the right auricle and auricular appendage is found greatly dilated. The muscle is hypertrophied so that the average thickness of the auricle is 2 mm. The right ventricle has a thin wall, about 1.5 mm. in thickness, contain-

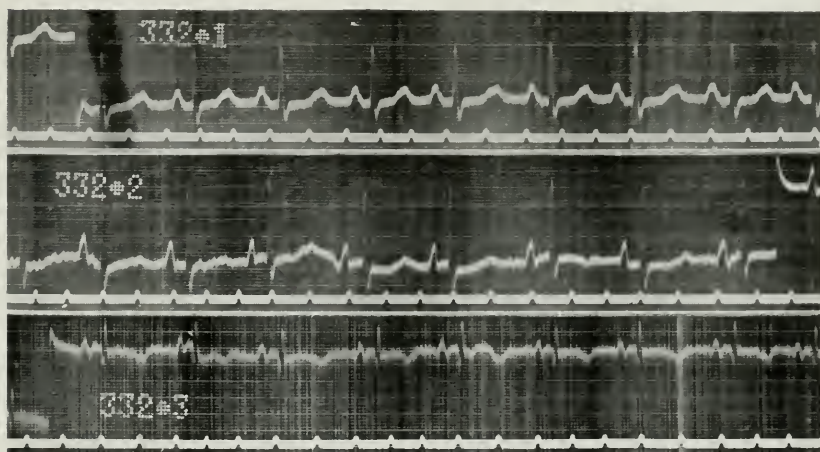


Fig. 2 (Case 2).—Patent foramen ovale; right ventricular atrophy; S wave in Lead I not increased.

ing very little muscle and abundant gray fibrous tissue. The pulmonary and tricuspid valves appear to be normal. The left auricle has an average thickness of 1 mm. The endocardium is gray. The foramen ovale is widely patent, having an orifice approximately 1 cm. in diameter. It is partly closed by a valve-like membrane, from the edge of which a fibrous cord passes to the wall of the left auricle. The aortic and mitral valves are normal. The left ventricle has an average thickness of 8 mm. The endocardium is gray and fibrous in appearance and there are gray markings in the muscle suggestive of fibrous tissue. The ductus arteriosus measures about 2 mm. in diameter. The lumen admits a probe about 0.5 mm. in diameter. The liver is very large, the spleen small.

COMMENT

The heart in this case was of a type of congenital malformation that is comparatively rare, there being only a few cases on record. The only other case from which electrocardiograms were made is mentioned by Einthoven,⁵ but the publication of the electrocardiograms and notes on the heart has not yet

appeared. He mentions that the electrocardiograms were normal. In the case under discussion it will be noticed that the P wave (Fig. 2) is considerably larger than normal, indicative of the marked auricular hypertrophy found in the heart. This is in accordance with the view usually held that auricular hypertrophy is associated with increased amplitude of the P wave. Lead I suggests the left ventricular hypertrophy, but this is not borne out in Lead III, in which the S wave is entirely absent. The left ventricular hypertrophy found at necropsy is not very great, but, in proportion to the amount of muscle tissue in the right ventricle, evidence of left ventricular hypertrophy should be expected in the electrocardiogram. Lewis has suggested that evidence of right or left ventricular hypertrophy in the electrocardiograms depends not so much on the absolute as on the relative increase of the muscle tissue above the normal in one or the other chamber. What is more important in this case is that there is a congenital malformation of the heart in which the S wave in Lead I is not deepened, the point that has been insisted on as necessary for a diagnosis of congenital malformation of the heart. This exception apparently depends on the atrophy of the right ventricle that was found to exist at necropsy.

The patients in cases 3 to 12, inclusive, are still alive and continue to show signs suggesting more or less strongly a congenital malformation of the heart. The cases are reported in brief, for they further bear out the opinion that congenital malformations of the heart pro-

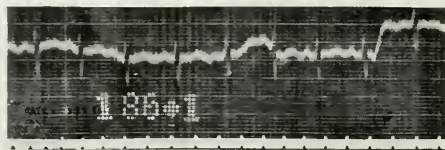


Fig. 3 (Case 3).—(Only Lead I obtained.) Pulmonary stenosis; right ventricular hypertrophy.

duce a deep S wave in Lead I of the electrocardiograms only when a right ventricular hypertrophy exists in consequence of the anomaly. It is fully realized that an attempt to diagnose a congenital heart malformation is uncertain at best and often erroneous. It is usually reasonably certain that a malformation exists, but the exact nature of such a lesion very often is open to discussion. It is especially true that two or more lesions are prone to occur in the same heart.

CASE 3 (Washington University Dispensary No. 16128).—L. D., boy, aged 10 months, was brought to the clinic for heart trouble. A diagnosis of congenital malformation of the heart and pulmonary stenosis was made. It was stated that the child had been a blue baby and subsequently had had repeated attacks, during which he became blue and the heart beat too fast and too hard. On examination there was noted cyanosis, mild clubbing of the fingers, a heart enlarged to the right, and there was a faint systolic murmur heard all over the precordium, best at the base.

Electrocardiograms (No. 186, Fig. 3) were made Oct. 12, 1915. They showed a rate of 158.8 per minute; conduction time Lead I, 0.118 second, with mechanism normal. Only Lead I was obtained.

STRENGTH OF CURRENTS IN CASE 3

	Millivolts
Lead I	R wave = 0.38
	S wave = 0.60

CASE 4 (Washington University Dispensary No. 16406).—M. W., aged 20 months, was received and a clinical diagnosis of congenital malformation of the heart and pulmonary stenosis was made. It was stated that at the age of 3 months it was noticed that the child became blue. There was a history of "jerking spells," the description of which resembled petit mal. Examination showed distinct cyanosis of lips, face, toes, fingers and nails. The heart dulness extended 2 cm. to the right of the midsternal line. A rough systolic murmur could be heard, loudest over the cardiac base, also in the back and all over the precordium. Roentgen-ray examination showed the heart only slightly enlarged to the left, moderately so to the right.

Electrocardiograms (191, Fig. 4) were made Oct. 18, 1915, showing rate 141.5 per minute; conduction time Lead II, 0.123 second, with mechanism normal.

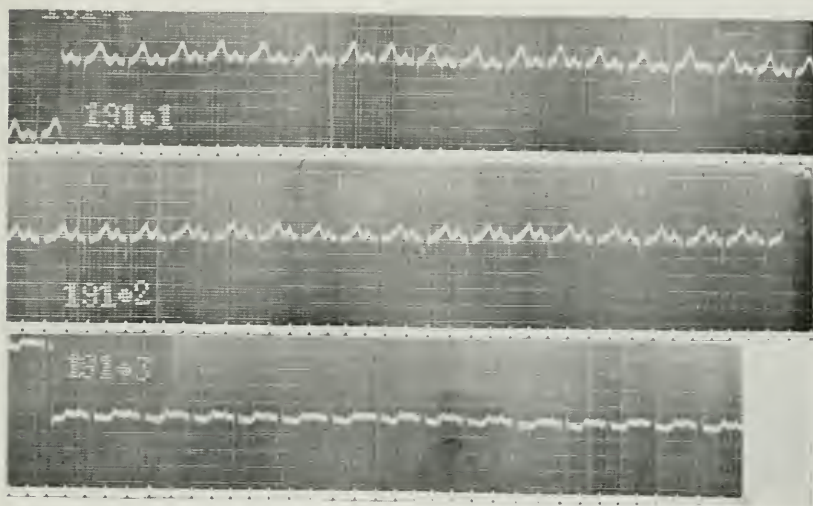


Fig. 4 (Case 4).—Pulmonary stenosis; right ventricular hypertrophy.

STRENGTH OF CURRENTS IN CASE 4

	Millivolts
Lead I	R wave = 1.11
	S wave = 1.50
Lead II	R wave = 1.98
	S wave = nil
Lead III	R wave = 2.80+
	S wave = nil

CASE 5 (Children's Hospital No. 9532).—F. B., boy, aged 10 years, was admitted to the hospital Dec. 3, 1915, with typhoid. A diagnosis of congenital malformation of the heart, pulmonary stenosis, defect of interauricular or ventricular septum. Blood culture and Widal reaction were positive. The boy had been a blue baby since birth, but had not had any convulsions. On exami-

nation he showed a marked cyanosis of all mucous membranes and skin. There was high-grade clubbing of all fingers and toes. The heart dullness extended 8 cm. to the left and 2.5 cm. to the right of the midsternal line. Over the entire precordium, best at the base, was heard a long, harsh systolic murmur, which was transmitted to the axilla, very faintly to the back, but not heard in the vessels of the neck. A very faint thrill could be felt over the pulmonic area. The liver was 2 cm. below the costal margin. The spleen could not be felt except during the first stages of the typhoid. The optic disks were moderately congested, and the retinal arteries were full and wavy, with the veins engorged, dusky blue and tortuous. No signs of atrophy in the disk or retina could be seen. Roentgen-ray examination showed a moderate enlargement of the heart both to the right and to the left. The red blood cell count was 6,200,000, hemoglobin 120 per cent. (Sahli). He was discharged from the hospital Jan. 4, 1916, recovered from the typhoid, the heart condition being the same, having had no apparent influence on the course of the typhoid.

Electrocardiograms (265, 271 and 336, Fig. 5) were made Dec. 3, 1915, to Jan. 23, 1916. These showed a rate of 121.7 per minute; conduction time Lead II, 0.169 second, with mechanism normal except for a slight delay in conduction during the typhoid.

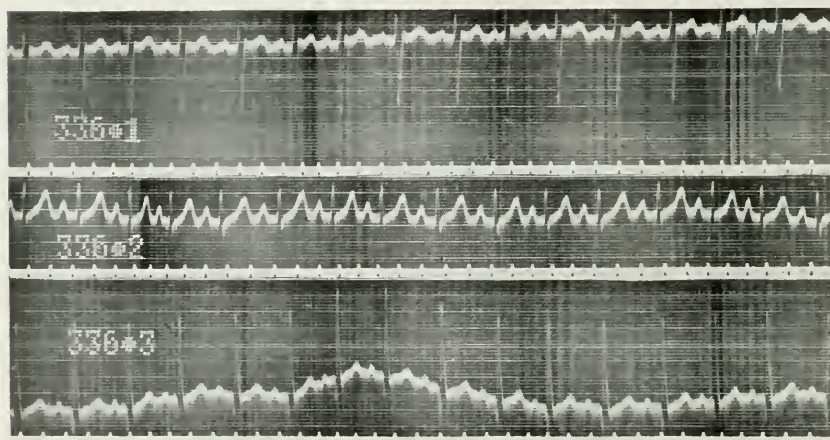


Fig. 5 (Case 5).—Pulmonary stenosis; right ventricular hypertrophy.

STRENGTH OF CURRENTS IN CASE 5

	Millivolts
Lead I	R wave = 0.60
	S wave = 2.10
Lead II	R wave = 0.87
	S wave = nil
Lead III	R wave = 2.54
	S wave = nil

CASE 6 (Children's Hospital No. 9535).—M. S., aged 9 years, was admitted to the hospital Dec. 4, 1915, for treatment for the heart condition. A diagnosis of congenital malformation of the heart, pulmonary stenosis and defect of the interauricular or ventricular septum was made. The child had been blue since birth, and with this condition was associated moderate dyspnea on exertion.

She also had fainting spells quite frequently. On examination she showed marked cyanosis of all mucous membranes and skin, and high-grade clubbing of all fingers and toes. There was a bulging of the precordium. A very faint thrill could be felt over the pulmonic area. The heart dulness extended 9.5 cm. to the left and 3 cm. to the right of the midsternal line. A long, rough systolic murmur could be heard everywhere, best over the base of the heart, transmitted to the axilla and distinctly heard in the left back. A very faint systolic murmur could be heard in the vessels of the neck. The liver was 2 cm. below the costal margin. The spleen could not be felt. The optic disks were markedly congested, the retinal arteries full, dark red and wavy and looked like veins. The veins were engorged, tortuous and dusky blue in color. No atrophy of disks or retina could be seen. Red blood cell count was 6,500,000, hemoglobin 115 per cent. (Sahli). Roentgen-ray examination showed a moderate enlargement of the heart shadow both to the right and left, especially the right.

Electrocardiograms (269 and 274, Fig. 6), made Jan. 4 and 10, 1915, showed a rate of 104.6 per minute; conduction time Lead II, 0.146 second, with mechanism normal.

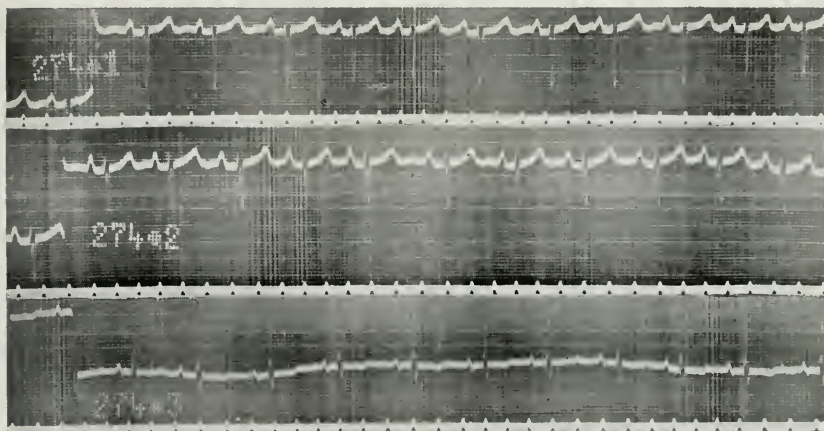


Fig. 6 (Case 6).—Pulmonary stenosis; right ventricular hypertrophy.

STRENGTH OF CURRENTS IN CASE 6

	Millivolts
Lead I	R wave = 0.10
	S wave = 1.46
Lead II	R wave = 0.30
	S wave = 1.20
Lead III	R wave = 0.55
	S wave = 0.20

CASE 7 (Washington University Dispensary No. 17548).—R. K., aged 8 years, was examined on entrance and a diagnosis of congenital malformation of the heart and defect of the auricular septum was made. There were no symptoms from the heart, and the condition was discovered during examination. There was no cyanosis or clubbing of fingers and no thrill over the heart. There was heard a loud systolic murmur all over the chest, best over the pulmonic area, but the expected enlargement to the right could not be made out on percussion.

Electrocardiograms (230, Fig. 7) were made Nov. 8, 1915, showing a rate of 97.1 per minute; conduction time Lead II, 0.174 second, with mechanism normal.

STRENGTH OF CURRENTS IN CASE 7

	Millivolts
Lead I	R wave = 0.60 S wave = 0.60
Lead II	R wave = 1.00 S wave = 0.60
Lead III	R wave = 0.55 S wave = 0.20

CASE 8 (Children's Hospital No. 9805).—E. P., boy, aged 23 months, was admitted to the hospital Feb. 3, 1916, for heart trouble. A diagnosis of congenital malformation of the heart and defect of the interauricular or ventricular septum was made. The child was a blue baby at birth and has had numerous periods during which he became blue, but has had no convulsions. He did not show any cyanosis or lividity. No thrill was perceptible over the heart. Heart

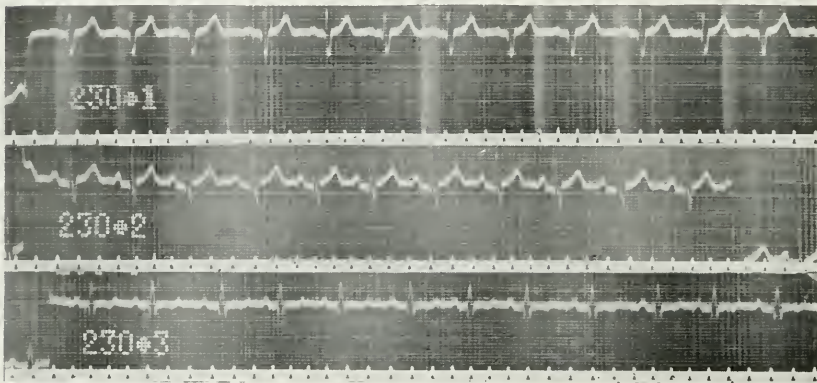


Fig. 7 (Case 7).—Defect of auricular septum; right ventricular hypertrophy.

dulness extended 1 cm. to the right and 5 cm. to the left of the midsternal line. There was a purring systolic murmur all over the heart area, most marked at the apex, transmitted to the axilla and back. The liver edge was at the costal margin. The red blood cells numbered 5,000,000. Roentgen-ray examination showed a heart enlarged markedly both to the right and to the left, and extending almost to the axilla.

Electrocardiograms (350, Fig. 8) were made Feb. 8, 1916, showing a heart rate of 75 per minute; conduction time Lead II, 0.188 second, with mechanism normal except for a slight delay in conduction. The curves suggest a left ventricular hypertrophy.

STRENGTH OF CURRENTS IN CASE 8

	Millivolts
Lead I	R wave = 1.08 S wave = 0.49
Lead II	R wave = 0.20 S wave = 0.20
Lead III	R wave = 0.20 S wave = 1.00

CASE 9 (Washington University Dispensary No. 20878).—J. C., aged 7 months, was brought to the clinic with pneumonia. A diagnosis of congenital malformation of the heart and defect of interauricular or ventricular septum was made as a result of a general examination. No cyanosis could be seen, but the

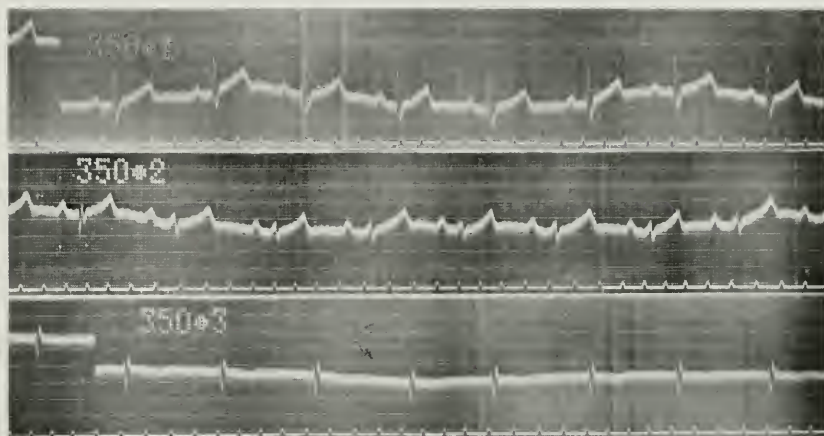


Fig. 8 (Case 8).—Defect of interauricular or ventricular septum; ventricular hypertrophy not evident in curves.

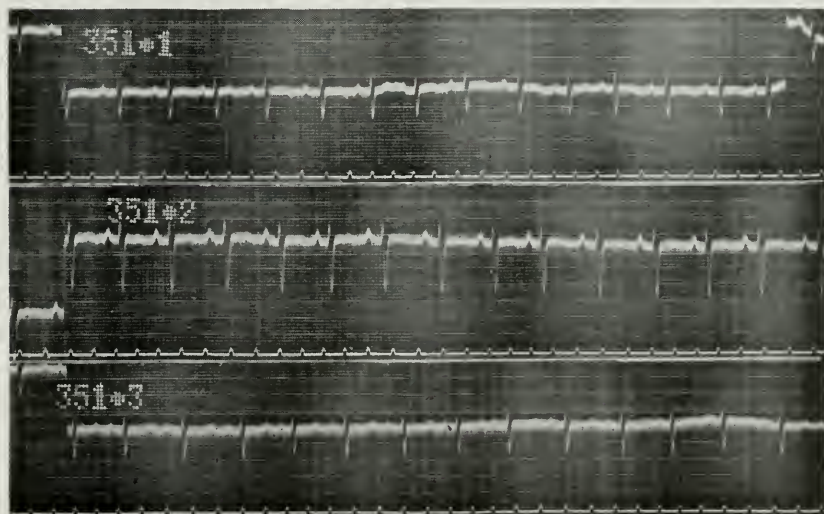


Fig. 9 (Case 9).—Defect of interauricular or ventricular septum; right ventricular hypertrophy (?).

skin at all times showed a marked lividity. No thrill could be felt over the heart. Dulness extended 2 cm. to the right and 5 cm. to the left of the midsternal line. A loud, rough systolic murmur could be heard all over the chest,

loudest to the left of the sternum about the third interspace. The liver was 4 cm. below the costal margin.

Electrocardiograms (351, Fig. 9) were made Feb. 10, 1916, showing heart rate 132.3 per minute; conduction time Lead II, 0.131 second, with mechanism normal.

STRENGTH OF CURRENTS IN CASE 9

	Millivolts
Lead I	R wave = 0.35
	S wave = 0.65
Lead II	R wave = 0.42
	S wave = 1.45
Lead III	R wave = 0.20
	S wave = 0.75

CASE 10 (Children's Hospital No. 9979).—L. McE., boy, aged 14 days, was admitted to the hospital March 12, 1916, when the heart condition was discovered and diagnosed as congenital malformation of the heart; consisting of a defect of the interauricular septum. Slight cyanosis was noticed the first

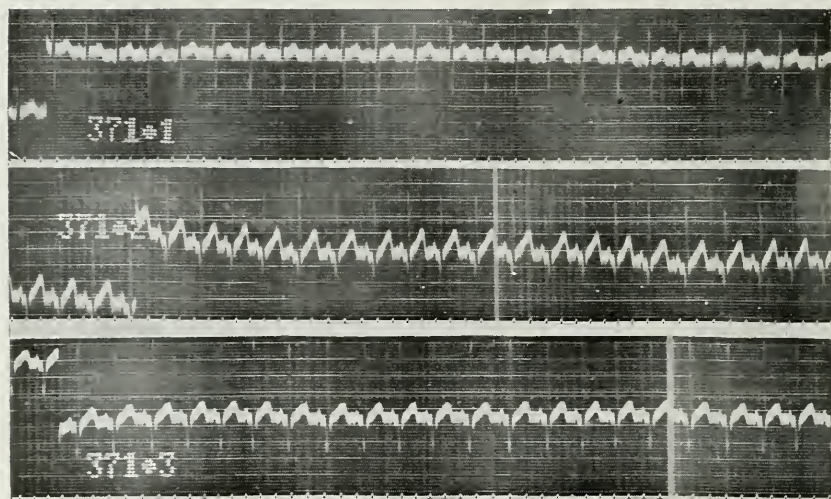


Fig. 10 (Case 10).—Defect of interauricular septum; right ventricular hypertrophy.

day of admission at several times, associated with shallow, slow respiration. But the cyanosis was not present constantly. No thrill could be felt. The heart dulness extended 2 cm. to the right and 5.5 cm. to the left of the mid-sternal line, a distinct increase, chiefly to the right side. A blowing systolic murmur could be heard all over the precordium, best at the base, not transmitted to the vessels of the neck or to the axilla. This murmur was rather indefinite at first, but before the patient's discharge, Feb. 23, 1916, it had become louder and more persistent. The red blood cell count was 3,232,000.

Electrocardiograms (371, Fig. 10) were made March 22, 1916, showing a heart rate of 132.3 per minute; conduction time, Lead II, 0.094 second, with mechanism normal.

STRENGTH OF CURRENTS IN CASE 10

	Millivolts
Lead I.....	R wave = 0.80 S wave = 1.10
Lead II.....	R wave = 1.74 S wave = nil
Lead III.....	R wave = 2.26 S wave = nil

CASE 11 (Washington University Dispensary No. 19191).—L. F., aged 21 years, was admitted and a diagnosis of congenital malformation of the heart, patent ductus arteriosus, chronic cardiac valvular disease, and auricular fibrillation was made. The patient had had indefinite joint pains at the age of 15, and moderate to marked dyspnea for the past several years. No cyanosis or clubbing of fingers was shown. A systolic thrill could be felt most marked over the pulmonic area. The heart dulness extended 5 cm. to the right and 13 cm. to the left of the midsternal line, a marked enlargement in both directions. There was a rough systolic murmur heard over the pulmonic area and trans-

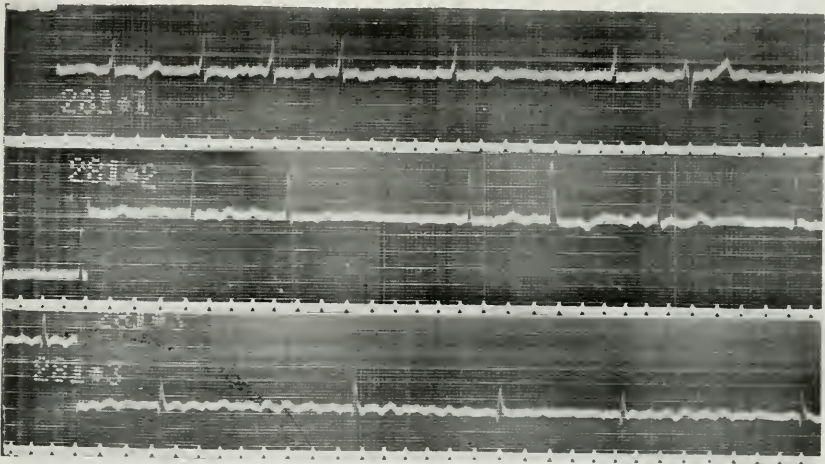


Fig. 11 (Case 11).—Patent ductus arteriosus; auricular fibrillation; right ventricular extrasystoles.

mitted down toward the apex, where a softer diastolic murmur could also be heard. At the apex a systolic murmur of a different pitch was perceptible, not transmitted very far into the axilla. In the axilla there was a rough diastolic murmur of different pitch and intensity. No murmurs were heard over the vessels of the neck. Fluoroscopic examination showed enlargement of the heart as made out by percussion. No auricular activity was seen.

Electrocardiograms (281, Fig. 11) was made Dec. 13, 1915, showing the heart rate to be 56.3 per minute, with coarse auricular fibrillation, ventricular extrasystoles, probably right sided.

STRENGTH OF CURRENTS IN CASE 11

	Millivolts
Lead I.....	R wave = 0.91 S wave = 0.20
Lead II.....	R wave = 1.35 S wave = nil
Lead III.....	R wave = 0.67 S wave = nil

CASE 12 (Washington University Dispensary No. 17559).—W. H., woman, aged 32 years, was admitted and on general examination a diagnosis of congenital malformation of the heart, consisting of patent ductus arteriosus was made. There was no history of her ever having been blue. For the previous eight or nine years, she had suffered from dyspnea on exertion, and her lips became blue at such times. Examination showed a bulging of the chest to the left of the sternum. The point of maximum impulse of the heart could not be made out. Heart dulness extended 4 cm. to the right and 11 cm. to the left of the midsternal line. A broad area of retrosternal dulness at the level of the first and second interspace was made out. Otherwise heart dulness was not enlarged. A rather distinct murmur could be heard at the apex, faint in the aortic area and over the vessels in the neck. There was no clubbing of the fingers. Roentgen-ray examination showed marked enlargement of the upper heart shadow on both sides, especially to the left. The aortic curve was increased.

Electrocardiograms (159, Fig. 12) were made Nov. 12, 1915, showing heart rate 69.3 per minute; conduction time Lead II, 0.159 second, with mechanism normal.

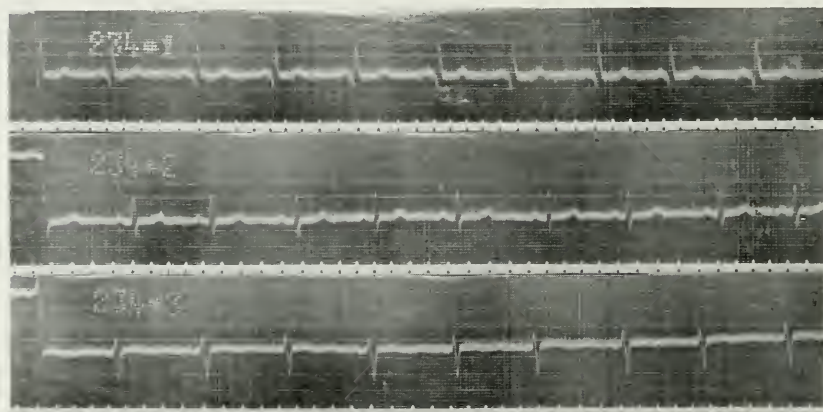


Fig. 12 (Case 12).—Patent ductus arteriosus; left ventricular hypertrophy.

STRENGTH OF CURRENTS IN CASE 12

	Millivolts
Lead I.....	R wave = 0.90 S wave = nil
Lead II.....	R wave = 0.70 S wave = 0.35
Lead III.....	R wave = 0.35 S wave = 0.80

In Cases 3, 4, 5 and 7 a diagnosis of pulmonary stenosis was made, with or without septal defects. It is well known that stenosis of the pulmonary orifice produces a high-grade right ventricular hypertrophy, and looking at the electrocardiograms of these four cases, one sees in each strong evidence in favor of a right ventricular preponderance, there being no doubt about the deep S wave in Lead I and the high R wave in Lead III. Of all the curves in this report, these show the

right ventricular hypertrophy most clearly and distinctively. Two of these curves were made from children nine and ten years old, and so were completely removed from any influence that the period of infancy might have in producing this type of an electrocardiogram. The other two are from children in the second year of life. Only from a larger group of cases could the conclusion be drawn that this type of curve is associated constantly with a stenosis of the pulmonary orifice or that such a curve is diagnostic of pulmonary stenosis.

In Cases 7, 8, 9 and 10 the heart lesion is considered to be a defect of the septum, auricular or ventricular, or both. In each one the evidence of right-side enlargement made out by physical signs is lacking, or it can be shown that the enlargement involves both sides of the heart. Case 10 is that of an infant 14 days old and the illustration is confused by the normal effect that this period of life has on the electrocardiogram. Cases 7 and 9 show curves very different from the group of hearts with pulmonary stenosis, the curves in these cases being in fact very similar to those in Case 1 in regard to the size of the R and S waves in Leads I and III. This is in agreement with the anatomical fact that defects of the septums are very apt to produce an enlargement of both right and left ventricles. In all the electrocardiograms of the second group of cases the evidence of a predominating enlargement of the right chamber, such as is found in the first group, is not so strong. The relation of right ventricular hypertrophy to defects of the septum and the form of electrocardiogram may be seen by comparing this group of four cases with Case 2. In that case there was a free communication between the two auricles, and yet, due to the small amount of muscle tissue in the wall of the right ventricle, that chamber failed to undergo a secondary hypertrophy. It is hardly possible that the form of electrocardiogram produced by these four cases could be associated so constantly with septal defects as to make them pathognomonic.

Of the last two cases, Case 11 is confused by the presence of a valvular lesion and auricular fibrillation, and it would be impossible to say from the curves whether one side or the other is hypertrophied. And by physical signs and Roentgen-ray examination both sides are made out to be enlarged, chiefly the left. In Case 12 there is distinct evidence of a left ventricular hypertrophy.

CONCLUSIONS

Twelve cases showing congenital malformation of the heart are reported, including four cases of pulmonary stenosis, five cases of defects of the interauricular or interventricular septums, two cases of patent ductus arteriosus, and one case of right ventricular atrophy.

Congenital malformations of the heart do not produce a distinctive electrocardiogram, but the type of curve will depend on the secondary effects of the heart chambers. This effect is chiefly on the right side of the heart, and malformations associated with a secondary relative right ventricular hypertrophy produce electrocardiograms with deep S waves in Lead I and high R waves in Lead III. Malformations not producing right ventricular hypertrophy fail to cause a characteristic change in the electrocardiogram.

Electrocardiograms are of value in the study of congenital heart disease in that they throw additional light on the relations of the chambers of the hearts, and so may be of aid in determining the type of lesion present.

DIPHTHERIA IN THE FIRST YEAR OF LIFE*

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Though the occurrence of diphtheria in the first year of life was noted by Bretonneau,¹ who first gave the name to the disease, all authorities are agreed as to its rarity at this period. During the last fifteen years the percentage of diphtheria patients under one year admitted to the Metropolitan Asylums Board's Hospitals² has remained fairly constant, varying between 1.5 and 2.8 per cent. annually of the total cases admitted.

The figures given by some continental observers are slightly higher. Thus Flügge³ states that among 6,394 cases of diphtheria in Breslau in the period 1886 to 1890, 160 patients, or 2.5 per cent., were under 1 year.

According to Filatow⁴ the morbidity in southern Russia among children below 12 months was 4 per cent. of the total. In the Children's Hospital directed by Baginsky⁵ in Berlin infants under 1 year formed 5.5 per cent. of the total number of diphtheria patients admitted; 1.4 per cent. occurring in the first six months and 4.3 per cent. in the second six months.

Several explanations of the rarity of diphtheria in the first year of life have been offered. It has been variously attributed to immunity acquired in utero, to antitoxin transmitted through the mother's milk (Schmid and Pflanz⁶), to the acid reaction of the secretions in the buccal cavity of the infant, which is inimical to the growth of the bacilli (Monti⁷) and to the greater care and comparative isolation which the nursing as a rule enjoys (Jacobi⁸). Though decidedly more frequent in the artificially fed than in infants at the breast, diphtheria in the latter is by no means unknown. In addition to numerous isolated cases in the literature, epidemics of diphtheria in sucklings have been reported by Siredey⁹ in 1877 at the Hôpital Larieboisière in Paris, and by Schlichter¹⁰ in 1892 and Riether¹¹ in 1897 at foundling hospitals in

* Submitted for publication April 18, 1916.

1. Bretonneau: *Memoirs on Diphtheria*, New Sydenham Society, 1859.

2. Metropolitan Asylums Board Reports, 1888 to 1914.

3. Flügge: *Ztschr. f. Hyg.*, 1894, xvii, 429.

4. Filatow: Quoted by Moltschanoff, *Jahrb. f. Kinderh.*, 1907, lxxv, 64.

5. Baginsky: *Diphtherie und diphtheritische Croup*, 1913.

6. Schmid and Pflanz: *Wien. klin. Wchnschr.*, 1896, ix, 955.

7. Monti: *Allg. Wien. med. Ztschr.*, 1896, xli, 1.

8. Jacobi: *Twentieth Century Practice of Medicine*, 1899, xvii, 78.

9. Siredey: *Thèses de Paris*, 1877, No. 337.

10. Schlichter: *Arch. f. Kinderh.*, 1892, xiv, 129.

11. Riether: *Wien. klin. Wchnschr.*, 1897, x, 666.

Vienna. Associated with the low morbidity is a high mortality. During the fifteen years, 1900 to 1914, the mortality among patients at this age in the Asylums Board Hospitals has ranged from a minimum of 14 per cent. in 1910 to a maximum of 41.4 in 1909, with an average of 32.1 per cent. as compared with a total mortality for all ages which has varied between 6.5 per cent. and 12.5 per cent. during the same period.

Though the mortality in the first year of life still remains regrettably high, it compares favorably with that in the preantitoxin era. Thus, the mortality in the Asylums Board's Hospitals in the period 1888 to 1893 was 69.9 per cent. for 146 patients under 1 year, and 31.3 per cent for 7,932 patients of all ages.

The mortality is always heaviest in the cases which require tracheotomy or intubation. In preantitoxin times recovery after surgical interference was quite exceptional at this age, as in the cases of Scoutteten,¹² who tracheotomized his own daughter, aged 6 weeks, and of Elias,¹³ who successfully tracheotomized two children, aged 8½ months and 10 months, respectively. Of thirty-seven infants under 1 year who were tracheotomized at the Berlin University Surgical Clinic between January, 1884, and July, 1894, not one survived (Hirsch¹⁴).

Since the introduction of antitoxin the mortality rates both for tracheotomy and intubation are still high, though they show a considerable improvement over those of the preantitoxin era. Thus, among 129 infants under 1 year tracheotomized for diphtheria in the Asylums Board Hospitals between 1900 and 1909, the mortality was 69 per cent., and among nineteen intubated, 63.2 per cent. Among twenty-one infants of this age intubated at the Moscow Children's Hospital between 1895 and 1904, the mortality was 52.4 per cent. (Moltchanoff¹⁵).

Montefusco's¹⁶ statistics are more satisfactory still. At the Ospedale Cotugno at Naples between 1902 and 1907 there were only twenty deaths among forty-five infants intubated for diphtheria, a mortality of 44.4 per cent.

Several writers have drawn attention to the importance of congenital syphilis as a predisposing cause of diphtheria in the infant. Not only is the general resistance to infection weakened, but the nasal fossae, already the seat of rhinitis, serve as a *locus minoris resistentiae*.

12. Scoutteten: Ann. de méd. belges, 1844, ii, 58.

13. Elias: Deutsch. med. Wchnschr., 1878, iv, 555.

14. Hirsch: Arch. f. klin. Chir., 1895, xlix, 894.

15. Moltchanoff: Jahrb. f. Kinderh., 1907, lxxv, 64.

16. Montefusco: La Pediatria, 1908, xvi, 82.

The present paper is based on a study of 2,600 consecutive cases of diphtheria that have been under my care at the Grove Hospital, London, in the course of the last twelve years. Of these, only twenty patients, or less than 1 per cent., were in the first year of life. Their exact ages were as follows:

5 weeks.....	1 case	7 months.....	2 cases
6 weeks.....	2 cases	8 months.....	3 cases
10 weeks.....	1 case	9 months.....	3 cases
11 weeks.....	1 case	10 months.....	1 case
5 months.....	2 cases	11 months.....	4 cases
<hr/>		<hr/>	
Total	7	Total	13

Thus, nearly twice as many occurred during the second half as during the first six months of the year. Eight were males, twelve were females. The cases are classified in four groups, according as the throat, nose and larynx were attacked separately or in combination.

1. Purely faucial: very severe, 1; severe, 1; moderately severe, 1; moderate, 1; mild, 1; total, 5.

2. Purely nasal: severe, 1; moderate, 2; mild, 3; total, 6.

3. Purely laryngeal: moderate, 1.

4. Multiple lesions: very severe faucial and nasal, 1; severe faucial, nasal and cutaneous, 3; severe faucial and nasal, 1; severe faucial and nasal, mild laryngeal, 1; moderate faucial, nasal and laryngeal, 1; mild faucial, mild laryngeal, 1; total, 8.

Table 1 gives a brief summary of each case. Particularly remarkable is the high percentage of cases with nasal involvement. Whereas of the total 2,600 only 668, or 25.6 per cent., showed any localization of diphtheria in the nose, thirteen cases, or 65 per cent., of the infants under 1 year showed nasal diphtheria either alone or in association with other diphtheritic lesions elsewhere. On the other hand, the disease was by no means confined to the nose, even in some of the youngest infants, as an equal number of children showed some faucial membrane.

The unusual frequency of cutaneous diphtheria is also striking, namely, 15 per cent., as compared with 1.1 per cent. in the total 2,600 cases. In two cases the skin in the immediate neighborhood of the mouth or nostrils was affected, and in one, which I have discussed at length elsewhere,¹⁷ the labium majus and skin around the anus. In only four was the larynx affected, in three of whom faucial membrane was also present. One required tracheotomy and died, the other three recovered.

In only three out of the twenty cases could the source of infection be detected. One girl, aged 5 months, with a moderate attack of nasal diphtheria of six days' duration, had probably been infected by her

17. Rolleston, J. D.: *Lancet*, London, 1910, ii, 947; *Brit. Jour. Child. Dis.*, 1914, xi, 209.

TABLE I.—SUMMARY OF TWENTY DIPHTHERIA CASES GIVING CHARACTER OF ATTACK, TREATMENT AND RESULT

No.	Age, Mos. ^a	Sex	Character of Attack	Dose of Serum	Serum Phenomena	Complications	Result
1	5	♀	Severe nasal	4,000	Death
2	6	♀	Mild nasal	4,000	Circhate 1 days; erythema...	Congenital syphilis, bronchopneumonia	Recovery
3	6	♀	Severe faucial, nasal and cutaneous..	12,000 12,000 12,000	Palatal palsy, cardiac palsy.....	Death
4	10	♂	Mild nasal	4,000	Congenital syphilis	Death
5	11	♂	Moderate nasal	4,000	Recovery
6	5	♂	Moderate nasal	12,000	Urticaria 2 days.....	Recovery
7	5	♂	Mild faucial	4,000	Congenital syphilis	Death
8	7	♀	Mild nasal	1,000	Recovery
9	7	♀	Moderately severe faucial.....	12,000	Urticaria 5 days.....	Recovery
10	8	♀	Severe faucial, nasal and cutaneous..	18,000	Recovery
11	8	♂	Severe faucial	15,000	Bronchopneumonia	Death
12	8	♀	Severe faucial	18,000	Death
			Nasal and cutaneous.....	24,000	Palatal cardiac paralysis.....
13	9	♀	Severe faucial	15,000	Urticaria 2 days.....	Otitis, bronchopneumonia	Death
			Nasal and cutaneous.....	12,000	Death
14	9	♂	Moderate faucial	18,000	Tracheotomy, bronchopneumonia
			Severe laryngeal	18,000	Recovery
15	9	♀	Moderate faucial	12,000	Urticaria 2 days; circinate erythema 9 days; no pyrexia	Recovery
16	10	♀	Severe faucial and nasal.....	12,000	Albumin	Recovery
			Mild laryngeal	12,000
17	11	♂	Severe faucial and nasal.....	18,000	Urticaria; abscess at injection site; circinate erythema; joint pains; adenitis	Bronchopneumonia; relapse of diphtheria; scarlet fever	Recovery
18	11	♂	Moderate faucial	12,000	Albumin	Recovery
			Nasal and laryngeal	12,000
19	11	♀	Moderate laryngeal	8,000	Recovery
20	11	♀	Very severe faucial.....	18,000 18,000	Albuminuria; bronchopneumonia ..	Death

^a The age of the first five patients is given in weeks.

sister, who had had a sore throat fourteen days previously and at the time of the patient's admission was said to speak "as if she had marbles in her mouth," that is, was probably suffering from paralysis of the palate. Another girl, aged 5 months, with mild nasal diphtheria of one day's duration, was admitted on the same day as her father, two brothers, and her mother, by whom she was being suckled, all of whom had a mild attack. The third patient, a girl aged 9 months, was admitted on the first day of a moderate faucial attack. Her sister, aged 9 years, had been admitted two days previously, with severe faucial diphtheria, on the sixth day of the disease, together with her brother, aged 3 years, in whom the attack was mild.

Three patients showed unmistakable clinical signs of congenital syphilis and it is highly probable that if the Wassermann test had been performed, latent syphilis would have been revealed in several more. In two cases death was due less to the attack of diphtheria, which in each case was mild, than to the concurrent syphilis.

None of the cases had immediately followed measles, which is often an antecedent of nasal diphtheria. With the exception of case 9, a moderately severe attack which made an uncomplicated recovery, the infection in all the breast-fed babies was confined to the nose. Not only is diphtheria itself uncommon during the first year of life, but its characteristic complication, paralysis, is also rare. Only two cases occurred among the twenty, each being examples of precocious palatal and cardiac palsy in very severe faucial diphtheria. The incidence of paralysis among the 2,600 patients of all ages was 19.8 per cent. On the other hand, bronchopneumonia, which was noted in only 1.2 per cent. of the patients of all ages, occurred in six of the twenty cases, or 30 per cent., five of which terminated fatally.

The high mortality in my twenty cases—nine deaths, or 45 per cent.—was thus mainly due to bronchopneumonia, which caused five deaths; cardiac paralysis, responsible for two deaths, and congenital syphilis for two.

Treatment.—In accordance with the practice prevalent in most of the Asylums Board Hospitals, the doses of serum given were relatively high. The patients with mild attacks received from 1,000 to 4,000 units, those with moderate attacks from 8,000 to 12,000, and those with severe attacks 12,000 to 24,000 units in a single injection, which was in some cases repeated. The highest total reached in any case was 42,000 units. With the exception of one patient, a boy of 11 months, who received 18,000 units for a severe faucial and nasal attack, and who developed, in addition to the ordinary urticaria, a circinate erythema, cervical adenitis, joint pains, and an abscess at the injection site, no serum manifestations of any severity were observed. As I have shown elsewhere the intramuscular method may be used in quite young children without any ill effects.

SUMMARY

1. Diphtheria in the first year of life is comparatively rare. Only twenty patients at this age occurred among a total of 2,600 diphtheria patients of all ages.

2. Congenital syphilis is an important predisposing cause.

3. Sixty-five per cent. showed some nasal involvement, with or without other diphtheritic lesions elsewhere, as compared with 25.6 per cent. in the total. Thirty per cent. were purely nasal, as compared with 1.5 per cent. of the total cases.

4. The mortality was high, 45 per cent., as compared with 7.3 per cent. in the total.

5. Paralysis was rare, two cases; bronchopneumonia, six cases, was common.

6. A history of infection was obtained in only three cases.

A METABOLISM STUDY OF A CASE OF DIABETES INSIPIDUS*

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AND

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INTRODUCTION

Diabetes insipidus may be divided into two types: (1) primary or idiopathic cases, including those cases in which there is no evident organic basis for the disease, and (2) symptomatic, including those cases in which some organic disease is present in the brain or elsewhere.

At the present time three theories as to the etiology of diabetes insipidus are held: (1) that it is due to a lack of ability of the kidneys to concentrate the urine; (2) that a primary polydipsia exists with normal kidney function; (3) that it is a polyuria, purely symptomatic in origin, produced by stimulation of the kidney by many causes, but in some cases by a hypersecretion of the hypophysis.

Erich Meyer¹ was the first to claim that the condition was due to a lack of ability of the kidney to secrete a concentrated urine. He showed that in normal individuals the ingestion of sodium chlorid was followed by a depression of the freezing point of the urine, indicating an increased molecular concentration, while in cases of diabetes insipidus the ingestion of sodium chlorid caused no depression of the freezing point, but an increase in the amount of urine excreted. Tallqvist,² Socin,³ and others agree with Meyer. Finkelnburg,⁴ Schwenkenbecher⁵ and Forschbach and Weber,⁶ from experimental evidence considered that in this condition the concentrating power of the kidney is not lost, but that the kidney is, under pathologic stimulation, excreting large amounts of urine. Schwenkenbecher also thinks that there exists an acquired tolerance for water on the part of the kidneys and rest of the

* Submitted for publication April 12, 1916.

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1. Meyer, Erich: *Deutsch. Arch. f. klin. Med.*, 1905, lxxiii, 1; *Deutsch. Klin.*, 1910, xiii, Supplement ii, 271; *Ztschr. f. klin. Med.*, 1912, lxxiv, 352; *Ueber den gegenwartigen Stand der Path. a. Ther. d. Diabetes insipidus*, Halle, 1914.

2. Tallqvist: *Ztschr. f. klin. Med.*, 1903, xlix, 181.

3. Socin: *Ztschr. f. klin. Med.*, 1913, lxxviii, 294.

4. Finkelnburg: *Deutsch. Arch. f. klin. Med.*, 1910, c, 33.

5. Schwenkenbecher: *München. med. Wehnschr.*, 1909, lvi, 2564.

6. Forschbach and Weber: *Ztschr. f. klin. Med.*, 1911, lxxxiii, 221; *Ibid.*, 1913, lxxvii, 153; see also, Günther: *Ztschr. f. klin. Med.*, 1914, lxxviii, 53, and Lichtwitz and Stromeyer: *Deutsch. Arch. f. klin. Med.*, 1914, cxvi, Nos. 1 and 2.

body in this disease, somewhat like the acquired tolerance for drugs that some individuals possess.

Engel⁷ considers that in diabetes insipidus there is present a prolonged nerve stimulation, possibly in the medulla, which excites the glomeruli to greater secretion or the tubules to diminished resorption or both. Stuber⁸ thinks diabetes insipidus is a manifestation of adrenalinemia, due to an increased function of the chromaffin system. Ebstein⁹ thought the condition was due to a primary polydipsia with a resultant polyuria.

Frank,¹⁰ on the basis of much study, considered that many cases of essential diabetes insipidus were caused by a hyperactivity of the pituitary, with resulting diuresis, as it has been shown by Schäfer and Herring¹¹ and many others that the secretion of the pituitary has a strong diuretic effect.

Cushing's¹² studies also point out the importance of this gland in relation to diabetes insipidus. Goldzieher,¹² Berblinger¹⁴ and Simmonds¹⁵ have pointed out relations between diabetes insipidus and lesions in and about the pituitary, especially its posterior part. Roemer¹⁶ reports experiments and clinical observations which tend to show that some cases of diabetes insipidus are due to a lack of secretion of the pars intermedia, and not to a hyperfunction of this gland.

Motzfeldt¹⁷ has published a very able summary of the literature in regard to diabetes insipidus and the pituitary, and reports three cases of diabetes insipidus in which nothing abnormal was found in the pituitary, but a number of symptoms pointed to an insufficiency of the posterior lobe of the pituitary.

Kahlmeter¹⁸ has also reviewed the literature regarding the relation between the pituitary and diabetes insipidus. Kleeblatt¹⁹ has recently described an interesting case of diabetes insipidus that followed trauma

7. Engel: *Ztschr. f. klin. Med.*, 1909, lxxvii, 112; *Maly's Jahrb. f. Tierchem.*, 1907, 858.

8. Stuber: *Deutsch. Arch. f. klin. Med.*, 1911, civ, 394.

9. Ebstein: *Deutsch. Arch. f. klin. Med.*, 1909, xcvi, 1.

10. Frank: *Berl. klin. Wchnschr.*, 1912, xlix, 393.

11. Schäfer and Herring: *Phil. T. Roy. Soc. London, Series B*, 1906, excix, 1.

12. Cushing: *The Pituitary Body and Its Disorders*, 1910.

13. Goldzieher: *Verhandl. d. deutsch. path. Gesellsch.*, 1913, xvi, 272.

14. Berblinger: *Verhandl. d. deutsch. path. Gesellsch.*, 1913, xvi, 281.

15. Simmonds: *München. med. Wchnschr.*, 1914, xl, 108.

16. Roemer: *Deutsch. med. Wchnschr.*, 1914, xl, 108.

17. Motzfeldt: *Norsk Mag. f. Lægevidensk.*, 1915, lxxvi, 1305; Barabo: *Ueber Diabetes insipidus mit Infantilismus*, Dissert., Munich, 1914; Dziembowski: *Ueber den ursächlichen Zusan. zwischen Hypophysis cerebri u. Diabetes insipidus*, Dissert., Breslau, 1914.

18. Kahlmeter: *Hygiea*, 1915, lxxvi, 1073.

19. Kleeblatt: *Med. Klin.*, 1915, xi, No. 33.

of the skull. Camus and Roussy²⁰ have reported extensive experiments which seem to show that the pituitary is not responsible for diabetes insipidus. Fitz²¹ has recently reported a very thoroughly studied case of diabetes insipidus in a boy of twelve and found that tests for renal function for the kidney as a whole were normal, but gave findings characteristic of vascular hyposthenuria, with vessels hypersensitive to chlorid stimulation. He found that the concentrating powers of the kidneys were not entirely lost.

CASE HISTORY

O. T., boy, aged 4 years, American, with one sister living and well, had no history of consanguinity, alcoholism, syphilis, tuberculosis or cancer. The patient had had no fall or injury, no childhood diseases. Labor was perfectly normal. About one year previously the patient had begun to void in bed. He drank water almost continually and voided about every twenty minutes. Except for these symptoms he appeared in perfect health.

The patient was well developed, of normal size and the color was good. There were no eruptions or adenopathies. The nose, mouth and pharynx, ears, eyes and cranial nerves were normal. The chest was small, round, symmetrical. No enlargement of the thymus could be made out. The lungs, heart, and abdomen were normal. His hands and feet were well formed. The genital organs were normal. No abnormalities were present in the nervous system. Temperature, pulse, and respiration were all normal.

The blood count showed erythrocytes, 3,800,000; hemoglobin, 68 per cent.; leukocytes, 7,000; polynuclears, 45 per cent.; small lymphocytes, 31 per cent.; large lymphocytes, 17 per cent.; eosinophils, 5 per cent.; basophils, 2 per cent.

The Wassermann reaction in the patient's blood and in that of his mother and father were negative. Roentgen-ray examination of the skull showed a normal sella turcica. The tuberculin and von Pirquet tests were negative.

EXPERIMENTAL

The plan of the experiment and the methods used for the estimation of the various substances in the food and excreta were the same as those described in previous papers.³² The chlorid estimations were made by Volhard's method, and the freezing point of the urine was determined by Beckmann's method.

The tables contain the results obtained in this study. During the nine days of study the patient retained 4.08 gm. of nitrogen. The urea nitrogen, ammonia nitrogen, amino-acid nitrogen, creatinin, uric acid, purin nitrogen and undetermined nitrogen are normal in amount and in the percentage of the total urinary nitrogen. The urinary acidity is also normal.

Vannini²³ in one case found the urea nitrogen 86.1 per cent., in another 90.66 per cent. of the total urinary nitrogen. Butler and

20. Camus and Roussy: *Presse méd.*, 1915, xlv, 517.

21. Fitz: *Arch. Int. Med.*, 1914, xiv, 706.

22. Rosenbloom: *Am. Jour. Med. Sc.*, 1911, cxlii, 7; *Ibid.*, 1913, cxlvi, 731; *Ibid.*, 1914, cxlviii, 65; *Arch. Int. Med.*, 1913, xii, 276; *Ibid.*, 1914, xiv, 263.

23. Vannini: *Berl. klin. Wchnschr.*, 1900, 638.

French²⁴ found it 94.96 per cent. Von Jaksch,²⁵ however, found very peculiar figures for the urea nitrogen in a case he studied. More than half the entire urinary nitrogen was excreted as amino-acid nitrogen, with a correspondingly low amount of urea nitrogen. The ammonia and uric acid figures have been found normal in previous studies.²⁶

With an increase in the nitrogen intake on the sixth day of the metabolism study, it may be noted that there was a consequent increase in the amount of nitrogen excreted in the urine, showing that the kidneys were perfectly capable of excreting increased amounts of nitrogen.

TABLE 1.—THE NITROGEN METABOLISM—

Day	Volume, C.c.	Total Acidity in C.c. of N/10 NaOH to Neutralize 24 Hours' Urine, C.c.	Total Nitrogen, Gm.	Urea Nitrogen		Ammonia Nitrogen		Amino-Acid Nitrogen		Creatinin		
				Gm.	Per Cent. of Total Nitrogen	Gm.	Per Cent. of Total Nitrogen	Gm.	Per Cent. of Total Nitrogen	Gm.	Nitrogen, Gm.	Nitrogen in per Cent. of Total N
1	1,890	113.4	5.9	5.0	84.7	0.254	4.3	0.059	1.0	0.278	0.101	1.7
2	3,080	240.2	9.1	7.6	83.5	0.379	4.2	0.1092	1.2	0.384	0.140	1.5
3	3,360	209.4	7.6	6.3	82.9	0.345	4.5	0.1064	1.4	0.406	0.148	1.9
4	4,060	192.0	8.8	7.2	81.8	0.437	4.9	0.1320	1.5	0.432	0.157	1.8
5	5,190	207.6	8.4	7.0	86.9	0.436	5.2	0.0924	1.1	0.561	0.204	2.4
6	4,305	301.0	11.2	9.4	83.9	0.687	6.1	0.1904	1.7	0.697	0.254	2.3
7	4,400	176.0	8.9	7.4	84.3	0.567	6.4	0.1602	1.8	0.536	0.195	2.2
8	4,260	153.4	12.4	10.3	83.1	0.561	4.5	0.1860	1.5	0.511	0.186	1.5
9	5,500	154.0	11.1	9.2	82.9	0.478	4.3	0.1554	1.4	0.612	0.223	2.0

A very interesting finding is the low percentage of nitrogen in the stool as compared to the nitrogen ingested. It shows a very complete absorption of the nitrogen intake, no doubt due to the increased ingestion of water, which Hawk²⁷ and his co-workers have shown lessens the amount of fecal protein excreted.

There has been considerable controversy regarding the protein²⁸ metabolism in diabetes insipidus. Some report the loss of protein in

24. Butler and French: *Guy's Hosp. Rep.*, 1904, lvii, 133.

25. Von Jaksch: *Ztschr. f. klin. Med.*, xlvii, 46.

26. Vannini, Butler and French, and von Jaksch, Footnotes 23, 24 and 25.

27. Hawk and Fowler: *Jour. Exper. Med.*, 1910, xii, 388; Mattill and Hawk: *Jour. Am. Chem. Soc.*, 1911, xxxii, 1999.

28. Tallqvist, Footnote 2; Vannini, Footnote 23; Butler and French, Footnote 24; Strubell: *Deutsch. Arch. f. klin. Med.*, 1899, lxxxix, 62; Hirschfeld: *Fest. f. Salkowski*, 1904, 187; Gerhardt: *Nothnagel's Spec. Path. u. Ther.*, 1900, vii, 7; Ferranini: *Jahresb. ü d. Leistung. in d. ges. Med.*, 1902 ii, 52.

this disease, in spite of a diet of sufficient caloric and nitrogen value. Others claim that the state of nutrition undergoes no important change which is also true of the protein metabolism. From our experiments in this case we would agree with this conclusion, as does also Gerhardt.²⁹

When a normal individual on a standard diet containing a definite quantity of sodium chlorid receives in addition from 10 to 15 gm. of sodium chlorid, the sodium chlorid concentration in the urine increases, while the total volume of urine excreted varies slightly, if at all. In a patient with diabetes insipidus, however, increasing the sodium

—AND URINARY NITROGEN PARTITION

Uric Acid			Purin Nitrogen		Undetermined Nitrogen		Feces Nitrogen		Balance	
Gm.	Nitrogen, Gm.	Nitrogen in per Cent. of Total N	Gm.	Per Cent. of Total Nitrogen	Gm.	Per Cent. of Total Nitrogen	Gm.	Per Cent. of Nitrogen Intake	Nitrogen Intake, Gm.	Nitrogen Balance, Gm.
0.042	0.014	0.24	0.004	0.07	0.468	7.9	0.30	4.9	6.1	-0.10
0.048	0.016	0.17	0.0087	0.095	0.85	9.3	0.45	5.4	8.3	-1.25
0.048	0.016	0.21	0.0044	0.058	0.68	8.9	0.33	3.7	9.0	+1.07
0.039	0.013	0.15	0.0148	0.160	0.85	9.6	0.42	5.1	8.2	-1.02
0.081	0.027	0.32	0.0141	0.167	0.63	7.5	0.40	4.4	9.1	+0.30
0.060	0.020	0.18	0.023	0.20	0.63	5.6	0.53	4.3	12.2	+0.47
0.057	0.019	0.21	0.012	0.14	0.55	6.2	0.41	3.2	13.0	+3.69
0.060	0.020	0.16	0.014	0.11	1.13	9.1	0.51	3.9	12.8	-0.11
0.099	0.033	0.30	0.020	0.18	0.90	8.9	0.56	4.5	12.2	+0.55

chlorid of the diet does not increase the sodium chlorid concentration of the urine, but in order to get rid of the excess of the salt, the quantity of urine excreted is greatly increased.

The significance of the results tabulated in Table 2 can be appreciated more readily when they are compared with Table 3 taken from Erich Meyers³⁰ article.

It may be readily noted from Table 2 that the concentration of sodium chlorid in the urine was not affected by the addition of 6 gm. sodium chlorid to the diet on the third day and the eighth day of the experiment. These results agree with those obtained by Meyer, showing that the kidneys of this individual have lost the normal power of concentrating the urine.

29. Gerhardt: Diabetes Insipidus, Modern Clinical Medicine, 1911, 113.

30. Meyer, Erich: Deutsch. Klin., 1910, xiii, Supplement No. 2, p. 271.

Garrod³¹ also mentions the fact that observations carried out by Roberts under Garrod's direction on children suffering from diabetes insipidus tend to confirm Meyer's results, which were based on adult cases.

TABLE 2.—THE CHLORID METABOLISM

Day	Volume of Urine, C.c.	Specific Gravity of Urine	Δ^* of Urine	Sodium Chlorid Content of Urine		Sodium Chlorid Intake, Gm.
				Gm.	Per Cent.	
1	1,890	1.005	0.24	2.08	0.110	3.4
2	3,080	1.005	0.22	3.38	0.110	3.5
3	3,080	1.005	0.25	3.32	0.108	9.5
4	4,000	1.003	0.27	4.10	0.102	3.4
5	5,190	1.002	0.22	5.36	0.103	3.4
6	4,305	1.002	0.26	4.70	0.109	3.4
7	4,400	1.002	0.28	4.40	0.100	3.4
8	4,260	1.003	0.24	4.66	0.109	9.6
9	5,500	1.002	0.22	5.56	0.101	3.5

* Freezing point of urine.

TABLE 3.—BEHAVIOR OF AN INDIVIDUAL WITH HEALTHY KIDNEYS ON THE ADDITION OF A SINGLE QUANTITY OF SODIUM CHLORID TO A STANDARD DIET

Volume of Urine, C.c.	Specific Gravity	Δ^* of Urine	Sodium Chlorid		Remarks
			Per Cent.	Grams	
1,375	1.011	0.78	0.198	2.72	10 gm. sodium chlorid added to diet
1,200	1.011	0.91	0.444	5.35	
1,700	1.012	0.88	0.374	6.36	
1,450	1.010	0.75	0.316	4.48	

* Freezing point of urine.

In the earlier literature it was claimed that the chlorid output is increased in diabetes insipidus. Oppenheim,³² however, shows that it has never been proved that this is due to anything but the sodium chlorid contained in the diet. Ferranini³³ has described two cases in which there was a marked increase in the excretion of sodium chlorid.

31. Garrod: In Diseases of Children, edited by Garrod, Batten, and Thursfield, 1914, 593.

32. Oppenheim: Ztschr. f. klin. Med., 1892, v, 618; Ibid., 1893, vi, 256.

33. Ferranini: Footnote 27.

TABLE 4.—THE SULPHUR METABOLISM AND URINARY SULPHUR PARTITION

Day	Total Sulphur, Gm.	Total Sulphate Sulphur		Etheral Sulphate Sulphur		Inorganic Sulphate Sulphur		Neutral Sulphur		Feces Sulphur, Gm.	Balance	
		Gm.	Per Cent. of Total Sulphur	Gm.	Per Cent. of Total Sulphur	Gm.	Per Cent. of Total Sulphur	Gm.	Per Cent. of Total Sulphur		Sulphur Intake, Gm.	Sulphur Balance, Gm.
1	0.49	0.42	85.7	0.03	6.1	0.39	79.6	0.07	14.3	0.14	0.80	+0.17
2	0.76	0.71	93.4	0.09	11.8	0.62	81.6	0.05	6.6	0.16	0.85	-0.07
3	0.55	0.50	90.9	0.06	10.9	0.44	80.0	0.05	9.1	0.17	0.82	+0.10
4	0.72	0.62	86.1	0.02	2.8	0.60	83.3	0.10	13.9	0.14	0.84	-0.02
5	0.71	0.63	88.7	0.02	2.9	0.61	85.8	0.08	11.2	0.22	0.98	+0.05
6	0.83	0.76	89.4	0.03	3.5	0.73	85.9	0.09	10.6	0.25	1.15	+0.05
7	0.79	0.72	91.1	0.02	2.5	0.70	88.6	0.07	8.9	0.23	1.14	+0.12
8	0.90	0.80	88.8	0.08	8.8	0.72	80.0	0.10	11.1	0.22	1.18	+0.06
9	0.71	0.61	85.9	0.05	7.0	0.56	78.9	0.10	14.1	0.24	1.09	+0.14

TABLE 5.—THE CALCIUM, MAGNESIUM, AND PHOSPHORUS METABOLISM

Day	Urine			Feces			Intake			Balance		
	Calcium Oxid., Gm.	Magnesium Oxid., Gm.	Phos-phorus, Gm.	Calcium Oxid., Gm.	Magnesium Oxid., Gm.	Phos-phorus, Gm.	Calcium Oxid., Gm.	Magnesium Oxid., Gm.	Phos-phorus, Gm.	Calcium Oxid., Gm.	Magnesium Oxid., Gm.	Phos-phorus, Gm.
1	0.177	0.056	1.13	0.54	0.06	0.70	0.82	0.103	1.90	+0.103	-0.013	+0.07
3	0.300	0.130	1.52	1.02	0.15	0.62	0.86	0.16	2.12	-0.52	-0.12	-0.02
3	0.196	0.072	1.31	0.61	0.09	0.64	0.72	0.18	2.16	-0.086	-0.013	+0.01
4	0.249	0.094	1.35	0.60	0.09	0.71	0.89	0.20	2.22	+0.041	+0.016	+0.16
5	0.183	0.086	1.41	0.57	0.08	0.65	0.55	0.20	2.24	+0.097	+0.034	+0.18
6	0.354	0.116	1.21	0.91	0.12	0.91	1.20	0.26	2.12	-0.064	+0.024	0
7	0.100	0.049	1.90	0.55	0.06	0.98	1.30	0.25	2.86	+0.25	+0.141	-0.02
8	0.100	0.051	1.75	0.88	0.06	0.92	1.21	0.20	2.82	+0.23	+0.089	+0.15
9	0.310	0.111	1.73	0.86	0.13	0.95	1.18	0.20	2.80	+0.02	-0.034	+0.12

Vannini and also ourselves have found a normal output of sodium chlorid in the urine.

It will be seen by Table 4 that in the nine days' study there was a retention of 0.60 gm. sulphur, as would be expected on account of the nitrogen retention.

The total sulphate sulphur, ethereal sulphate sulphur, inorganic sulphate sulphur, and neutral sulphur are normal in amount and in percentage of the total urinary sulphur. Vannini has also found that the excretion of sulphates runs parallel with that of the protein catabolism in this condition. He also found normal values for the urinary ethereal sulphates.

According to Table 5 in the nine days' study there was a retention of 0.71 gm. calcium oxid, 0.124 gm. magnesium oxid and 0.83 gm. phosphorus. The percentage distribution of calcium, magnesium and phosphorus in the urine and stool is normal in amount.

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A STUDY OF THE ETIOLOGY OF CHOREA*

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This study was undertaken primarily to determine, if possible, the parts which syphilis and bacterial infection play in the etiology of chorea. Several other subjects, such as the relative frequency of endocarditis and rheumatism in association with chorea and the frequency with which possible foci of infection, such as diseased tonsils and carious teeth, are present in chorea, have also been incidentally investigated. The spinal fluid has also been studied in a number of instances. Twenty-six children, eleven boys and fifteen girls, were studied, their ages varying between 3 and 11 years. One of the children died of chorea and several had a very severe type of the disease, but the course was mild or moderate in the remainder.

THE RÔLE OF SYPHILIS IN THE ETIOLOGY OF CHOREA

According to Flatau,¹ Kowalewsky was the first to call attention to the possible etiologic relation of syphilis to chorea. It was Milian,² however, who started the discussion of this question. He presented two girls with chorea, showing evidences of syphilis and having positive Wassermann reaction, before the Medical Society of the Hospital of Paris in 1912. Under syphilitic treatment one of these recovered promptly and the other improved. He argued from these cases that syphilis might be the cause of chorea. A few months later he³ reported the results of the Wassermann test in thirteen cases of chorea. It was strongly positive in five, partially positive in three, a total of 61.53 per cent., and negative in five. He also studied these cases and two others as to evidences pointing to hereditary syphilis and stigmata

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1. Flatau: *Arch. f. Psychiat.*, 1894, xxvi, 552.

2. Milian: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1912, Series 3, xxxiii, 955.

3. Milian: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1912, Series 3, xxxiv, 628.

of syphilis. He came to the conclusion that the evidence in favor of syphilis was certain in eleven, or 73.33 per cent., probable in two, or 13.33 per cent., and doubtful in two, or 13.33 per cent. The data on which he based his conclusions do not in many instances, however, justify these conclusions to the unprejudiced observer. His paper aroused much discussion, most of which was unfavorable. Comby argued that the presence of a positive tuberculin test would be as good evidence in favor of the tubercular origin of chorea as a positive Wassermann test of the syphilitic origin. He also argued that the fact that both chorea and syphilis are helped by arsenic shows nothing as to the syphilitic origin of chorea. Guillian said that the pathologic anatomy of chorea is not that of syphilis and that syphilis of the nervous system does not act like chorea.

Babonneix⁴ then looked over the histories of the last 145 cases of chorea in Hutinel's service and found reasons to justify the thought of congenital syphilis in only thirty-six, or 25 per cent. He remarks that these cases show little as to the etiologic relation of syphilis to chorea and calls attention to the fact that there was sufficient in the histories or physical examinations of the cases of pneumonia to justify a suspicion of syphilis in 18 per cent.

Grabois⁵ also tabulated Hutinel's cases, including those of the year following the study of Babonneix, and found thirty-four of 136 cases, or 25 per cent., in which syphilis might be thought of. Certain evidence of syphilitic inheritance was present in but three, or 2.2 per cent., while there was presumptive evidence in twenty-eight, or 20.5 per cent. The Wassermann test was positive in but one of the four cases in which it was tried. Moreover, rheumatism was present in 23.5 per cent. and heart disease in 32.3 per cent. of the cases of chorea in which syphilis might be suspected.

Milian⁶ continued his investigations and in 1914 was apparently of the opinion that all cases of chorea are syphilitic in origin. He argued, in connection with a case reported by Grenet and Sédillot⁷ that a negative Wassermann reaction does not exclude syphilis. A striking thing in all of Milian's work is the lack of Wassermann tests, which were very seldom made.

Comby,⁸ as the result of Milian's statistics and opinions, studied thirty-three cases of chorea in girls between 5 and 15 years of age,

4. Babonneix: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1912, *Séries 3*, xxxiv, 671.

5. Grabois: *Thèse de Paris*, 1913, No. 298.

6. Milian: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, *Séries 3*, xxxvii, 368.

7. Grenet and Sédillot: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1913, *Séries 3*, xxxv, 73.

8. Comby: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1915, *Séries 3*, xxxix, 238.

whom he treated and cured in 1913, 1914 and early 1915. Stigmata of syphilis were present in four and the mothers of seven others had had frequent miscarriages. The Wassermann test on the blood was positive in six, feeble or doubtful in four and negative in twenty-three. The cutaneous tuberculin test was positive in twenty and negative in eleven. He concludes that there is more reason for believing that latent tuberculosis is the cause of chorea than there is for attributing it to syphilis, and states that all that the positive Wassermann tests and the presence of a history suggestive of syphilis or of stigmata of the disease show is that a certain proportion of children with chorea also have syphilis. He does not deny that syphilitic infection may play a part in the production of chorea and believes that the encephalitis of chorea may be due to a variety of causes, among which may be syphilis.

Comby's⁹ results having been criticized on the ground that the Wassermann test is sometimes positive in the cerebrospinal fluid when it is negative in the blood; he tested both the cerebrospinal fluid and the blood in seven cases. The Wassermann test was negative in the cerebrospinal fluid in all, while it was positive in the blood in one. It is worthy of note in this connection that Marie and Chatelin* got negative tests in the cerebrospinal fluid in eight and Merklen¹⁰ in one case of chorea.

Koplik¹¹ made Wassermann tests on the blood in ten cases of chorea and got negative results in eight. The test was unsatisfactory, but not positive, in the others. There was nothing to suggest syphilis in the histories or physical examinations of any of them.

Salvarsan and Neosalvarsan Treatment.—Salvarsan was first used in the treatment of chorea because of the supposed favorable action of arsenic in this disease, on the basis that, this being the most powerful preparation of arsenic, it should give better results than the other forms of the drug. It was not long, however, before it was used because of the belief of some that chorea is a manifestation of syphilis. Much has been written about the use of salvarsan in this connection on a very slight basis of facts.

Salinger,¹² writing in June, 1912, was able to collect but ten cases treated with salvarsan, those of Bokay, Hainess, Mayerhofer, Dufour and Low, Hahn and his own. Szametz¹³ used it in one case, presumably not syphilitic, with good results, while Flatau¹⁴ used it ineffec-

* Reference given in Footnote 15.

9. Comby: Bull. et mém. Soc. méd. d. hôp. de Paris, 1915, Series 3, xxxix, 666.

10. Merklen: Bull. et mém. Soc. méd. d. hôp. de Paris, 1912, Series 3, xxxiv, 628.

11. Koplik: Arch. Pediat., 1915, xxxii, 561.

12. Salinger: München. med. Wchnschr., 1912, lviii, 25.

13. Szametz: München. med. Wchnschr., 1912, lix, 2333.

14. Flatau: München. med. Wchnschr., 1912, lix, 2102.

tually in a chronic case, unquestionably syphilitic, as the patient was relieved by mercury.

Marie and Chatelin¹⁵ treated twenty-five patients for chorea with intravenous injections of salvarsan, obtaining favorable results. In eight cases, in which the Wassermann test was tried with the cerebrospinal fluid, negative results were shown. They do not believe that the reason salvarsan does good in chorea is because chorea is syphilitic in origin, but because of the parasitocidal action of the arsenic.

Koplik¹¹ treated nine patients with neosalvarsan, getting no effect in seven; one developed nephritis, and another had a relapse.

A number of authors have claimed favorable results also from the use of salvarsan by the rectum. This method of treatment is hardly worthy of consideration in comparison with the intravenous method. If salvarsan and neosalvarsan are to be given at all, they should be given intravenously.

It seems clear, therefore, from a study of the literature, that there is very little evidence in favor of the syphilitic origin of chorea and much against it.

Original Investigations.—There was nothing whatever in the history of twenty-one, or 81 per cent., of our twenty-six patients to suggest syphilis. In the others there was a history of miscarriages, two in six pregnancies, one in eleven, one in four, four in five, and five in eleven pregnancies. No one of the patients was born prematurely. The blood of three of the five children in whose families there was a history of miscarriages gave a negative Wassermann test, the spinal fluid not being tested in these cases. The blood of one gave a positive Wassermann test; the spinal fluid was not tested in this instance. The blood of the other gave a doubtful reaction on three occasions, while the spinal fluid was negative at one examination. These two children were the only ones that gave either a positive or a questionable Wassermann test in the whole series.

None of the twenty-six children showed any stigmata of syphilis. The Wassermann test was done at the Wassermann laboratory of the Massachusetts State Board of Health on the blood of twenty-five of the twenty-six patients. It was negative in twenty-three, or 92 per cent. It was positive in one, and doubtful in another on three occasions. The Wassermann test was tried on the cerebrospinal fluid, obtained by lumbar puncture, on eight patients. It was negative in all.

Granting that a negative Wassermann test does not absolutely exclude syphilis, it is, nevertheless, very strong evidence against it, so strong that it practically excludes syphilis as the cause of the chorea

15. Marie and Chatelin: Bull. de l'Acad. de méd., Paris, 1912, Series 3, lxviii, 507.

in twenty-three of these patients. The case against syphilis as the cause of the chorea in these twenty-three children is further strengthened by the facts that none of them presented any of the stigmata of syphilis and in only three of them was there anything in the family history even remotely suggesting syphilis. The presence of a positive Wassermann reaction in one instance and a doubtful one in another does not prove that syphilis was the cause of the chorea in these children, because that proportion of positive and doubtful reactions is no higher than the average for the hospital class of children in Boston and vicinity, and probably not so high. Moreover, the test was negative in the spinal fluid of the child in whom the test was doubtful in the blood, when it would naturally be expected to be more marked in the spinal fluid than in the blood, if syphilis was the cause of the chorea. The spinal fluid was unfortunately not examined in the other case. Furthermore, as Comby has said, a positive Wassermann test in a child with chorea does not prove that the chorea is due to syphilis any more than a positive tuberculin test proves that it is due to tuberculosis. As a matter of fact, twenty-one, or 84 per cent., of the twenty-five children in this series in which the skin tuberculin test was done showed a positive reaction. It would be absurd to assume that tuberculosis was the cause of the chorea in these twenty-one children. A study of these cases justifies the conclusion, therefore, that syphilis seldom, if ever, plays an active part in the etiology of chorea.

THE RÔLE OF BACTERIA IN THE ETIOLOGY OF CHOREA

The close clinical relationship between acute articular rheumatism, endocarditis and chorea, taken in connection with the present conception that acute articular rheumatism and acute endocarditis are bacterial in origin, has suggested that chorea is also bacterial in origin and perhaps caused by the same or a similar organism. Further evidence pointing in the same direction is the frequency with which local foci of infection, notably in the tonsils or in and about the teeth, are found in all of these conditions. For these reasons an increasing number of investigations directed toward the discovery of such an organism or group of organisms have been undertaken during recent years.

Our patients confirm the general belief as to the frequency of the association of chorea with rheumatism and endocarditis, seven of them, or 37 per cent., having had rheumatism in the past or with the chorea. Six of them had acute endocarditis and six chronic valvular lesions, a total of twelve, or 46 per cent. They show also the frequency with which local foci of infection are found in the mouth and throat in chorea. The tonsils were normal in but eleven cases, while they were diseased in eleven, or 42 per cent., and had been removed on account of disease in four others. The teeth were normal in but seven and

were carious in nineteen, or 73 per cent. Pyorrhea was present in two of these children and definite pus pockets were found in three others when the teeth were extracted.

A number of investigators have found bacteria in the central nervous system in fatal cases of chorea. Among them may be mentioned Westphall, Wassermann and Malkoff,¹⁶ who isolated a diplococcus from the cerebrospinal fluid and with it consistently produced polyarthritis in rabbits. Poynton and Payne¹⁷ also isolated and cultivated a diplococcus from the cerebrospinal fluid in four cases of fatal rheumatism, in three of which there was chorea at the time of death. They produced twitching movements, arthritis, endocarditis and pericarditis by the intravenous injection of this organism into rabbits. They also demonstrated the presence of this same diplococcus three times in the cerebral pia mater and once in the brain in cases of chorea. They also found them in the brain and pia mater of a rabbit that had shown twitching of the muscles.

Bacteriology of the Blood in Chorea.—Other investigators have found micro-organisms in the blood during life. Camisa¹⁸ gives seventeen references to authors who have found microorganisms in the blood of patients with chorea. They were usually found in only one or, at most, three cases. The organisms found were very different—bacilli, staphylococci, diplococci, streptococci. He studied the blood taken from the veins in nine patients varying in age from 6 to 16 years. It is to be noted that they all showed evidences of cardiac lesions. He found a diplostreptococcus, forming short chains, in six cases. The morphologic and cultural characteristics of the organism were the same in all cases. The blood serum of patients with chorea at the height of the disease agglutinated this organism to a moderate degree, more than it did the ordinary pus streptococci. The agglutinating power of the blood diminished with improvement of the symptoms. This agglutinating power was not specific, however, as the organism was agglutinated more strongly by the serum of a typhoid patient. Animal experiments were negative. He believes that this organism is the cause of chorea, but admits that it is possible that chorea may also be caused by other organisms.

Donath¹⁹ studied seven cases of very severe chorea, two of which were fatal. He found the *Staphylococcus pyogenes-albus* in the blood in four cases and in the brain in one case, and the *Staphylococcus pyogenes-aureus* in the blood in one case and the cerebrospinal fluid in

16. Westphall, Wassermann and Malkoff: Berl. klin. Wchnschr., 1899, xxxvi, 638.

17. Poynton and Payne: Lancet, London, 1905, ii, 1760.

18. Camisa: Centralbl. f. Bakteriöl., Orig., 1910-1911, lvii, 99.

19. Donath: Ztschr. f. d. ges. Neurol. u. Psychiat., Orig., 1910-1911, iv, 91.

another. Animal experiments were inconclusive. He is inclined to think that the staphylococci found were of pathogenic significance, but does not ascribe any specificity to them.

Collins²⁰ obtained a pure culture of a diplococcus from the blood of a girl ill with chorea. This organism grew in twos and formed short chains of from four to six pairs. A vaccine was prepared from it, which, in his opinion, had a favorable influence on the course of the disease.

Richards²¹ made blood cultures from the veins in two cases of chorea. It is to be noted that one of the patients had chronic endocarditis, acute arthritis and pyorrhea alveolaris, while the other had chronic endocarditis and had had tonsillitis. He found the *Streptococcus viridans* in both. He says that there is "no doubt that this coccus found in the blood is associated with endocarditis, but that it is the etiologic factor sine qua non in chorea is not proved."

La F  tra²² in the discussion of a paper by Strauss stated that he had found the *Streptococcus viridans* in two cases of chorea at the Bellevue Hospital and that complement deviation tests were positive in two others. He does not state in how many instances he obtained negative results. Bartley, in the same discussion, stated that tests made in three or four cases at the Long Island College Hospital were negative.

Koplik¹¹ states that he has had the blood diligently cultivated in many cases of chorea, but that he has failed to isolate any organisms.

It is evident that the results thus far obtained from blood cultures in chorea are inconsistent and inconclusive. In almost every case in which organisms have been found there has been some other complicating condition amply sufficient to account for the presence of organisms in the blood. Their presence, therefore, has not proved that they were the cause of the chorea. The absence of organisms in the blood does not prove, however, that chorea is not caused by bacteria, because, although the cause of the disease, they may have been absent from the blood at the time the cultures were made, and the methods of cultivation used may not have been suitable for the growth of the organisms, if present.

Bacteriology of the Cerebrospinal Fluid in Chorea.—There are practically no data as to the bacteriology of the cerebrospinal fluid in chorea during life. Donath¹⁹ found the *Staphylococcus aureus* in one case, while Passini²³ found the cerebrospinal fluid sterile in five cases. Collins²⁰ has reported a case of chorea as cured by treatment with an

20. Collins: Brit. Med. Jour., 1913, i, 220.

21. Richards: Jour. Am. Med. Assn., 1914, lxii, 110.

22. La F  tra: Arch. Pediat., 1915, xxxii, 135.

23. Passini: Wien. klin. Wchnschr., 1914, xxvii, 1363.

autogenous vaccine prepared from a coccus obtained by lumbar puncture.

Original Investigations.—We have made during the past year a bacteriologic study of twenty-six cases of chorea in the acute stage of the disease with a view to determining the presence of an infecting agent in the blood stream and cerebrospinal fluid, the frequency with which it could be obtained, and its cultural characteristics. The cerebrospinal fluid was obtained by lumbar puncture under an anesthetic and with sterile precautions twenty times in nineteen cases. The blood was obtained from one of the veins of the arm with sterile precautions, sometimes under an anesthetic and sometimes not, thirty-one times in twenty-six cases.

About 5 c.c. of cerebrospinal fluid and 5 c.c. of blood were secured when it was possible. The blood was immediately put into a series of different kinds of mediums and incubated for two weeks. During this time frequent examinations of the cultures were made and fresh transfers were inoculated. The cerebrospinal fluid was similarly treated. The mediums used consisted of blood dextrose agar, Loeffler's blood serum, neutral and acid milk, serum water dextrose, lactose, and saccharose, dextrose bouillon, and at times hydrocele fluid alone and with agar. Aerobic and anaerobic methods were both used. Blood was also drawn into citrated saline solution and centrifuged. The sediment was planted and smears made for examination. In every instance the cultures, as well as smears from the cerebrospinal fluid, were negative. Blood cultures were negative in twenty-six instances, even after several weeks of incubation and subculturing. In five cases organisms were obtained. In one case a small bacillus, diphtheroid in type, appeared, giving a fine, pinpoint, moist growth on blood serum at the end of a week. This organism grew very slowly on agar and failed to produce any reaction in solutions of serum water containing saccharose, lactose, mannite, raffinose, dextrose, inulin, and maltose. It was gram negative and was not pathogenic for rabbits even when large doses were given intravenously. In this instance the tonsils were large and the teeth were slightly carious. The heart was normal and there were no rheumatic symptoms.

Diplococci were found in the blood smears in one case, but no organisms were cultivated. In this instance the tonsils were submerged and there were several carious teeth, one of which had a pocket of pus about its root. The heart was normal and there were no symptoms of rheumatism.

In two other cases short chains of cocci appeared in litmus milk in the initial culture, but all efforts of subculturing failed. The tonsils were normal in both of these cases, but the teeth were carious. The heart was normal in both and neither showed any evidences of rheumatism.

In another case positive blood serum cultures were obtained after ten days of incubation. In this instance the tonsils and adenoids had been removed, but the teeth were carious. The patient had acute endocarditis and had had several attacks of rheumatism. The first colonies appearing were flat, colorless and disklike. Smears showed these to be made up of long chains of a fine gram-positive streptococcus. Subcultures were at first obtained with difficulty. This organism produced a slight greenish-yellow zone of hemolysis on blood agar plates, fermented saccharose and dextrose in serum water cultures, did not acidulate or coagulate milk, and failed to act upon lactose, mannite, raffinose, inulin, and maltose. This organism is now readily subcultured and its early characteristics have remained unchanged through ten generations. Intravenous inoculations in two rabbits in doses of from 2 to 3 c.c. of a thick suspension of the organism killed the animals in from twenty-four to forty-eight hours. Necropsies showed a general septicemia, and cultures from the heart's blood and knee joints gave a good growth of streptococci. Four other large rabbits were given a series of intravenous inoculations of from 0.5 to 1 c.c. of a heavy suspension of the organism at an interval of from three to five days. Three were killed at intervals of from ten to thirty days. All the animals lost weight and, with the exception of Rabbit 6, which died after five days, they all showed lameness and difficulty in walking and standing and restlessness on handling of the joints. Some swelling of the knees was also noted.

PROTOCOLS

RABBIT 3.—Large white male, showing considerable loss of weight. Opening of the knee joint showed a smooth, glistening surface. There was a moderate amount of fluid in both joints, sticky and turbid. Smears showed numerous leukocytes and chains of streptococci. A good growth was obtained on culture.

The heart cultures gave streptococci. The organ was filled with postmortem clot, but the valves and endocardium were negative. The brain was not examined.

RABBIT 4.—A medium-sized brown male, showing marked loss of weight, was given four inoculations in three weeks' time, each dose consisting of 1 c.c. of saline suspension. The animal was killed while moribund. For two weeks there had been apparent pain and limitation of motion in both knee and hip joints. The knee joints showed a turbid, sticky fluid containing numerous leukocytes and streptococci. Cultures gave the organism in pure culture.

The heart was negative. Cultures from the heart's blood gave chains of streptococci.

The dural and pial vessels about the brain were much engorged. No thickening or exudation was found. Smears gave streptococci in chains, but cultures were negative. Sections were hardened in 80 per cent. alcohol and stained with hematoxylin, eosin and Giemsa stain. Marked round-cell infiltration of the pia extending slightly into the brain substance was noted. There was some increase of leukocytes. No organisms were found.

RABBIT 5.—A large brown and white female was given a series of intravenous inoculations of a heavy saline suspension of streptococcus over a period

of five weeks. Marked crippling of the joints of the fore and the hind legs was noted. The animal was killed while in fairly good condition. The heart valves and endocardium were negative. Smears and cultures from the heart's blood were negative. The pial vessels were slightly distended. Smears and cultures were negative. The knee joints both contained a thick, sticky fluid, the left capsule being distended with it. Smears showed numerous leukocytes and chains of streptococci. Cultures of streptococci were readily obtained. Sections of the brain showed marked round-cell infiltration of the pia over the cortex and extending generally into the convolutions. No organisms were seen.

RABBIT 6.—A large, white male rabbit was given 1.5 c.c. intravenously of a heavy saline suspension of streptococci obtained from the knee joint of Rabbit 5. The animal lived four days and then died. The heart showed some enlargement. The valves were negative macroscopically. Scattered over the endocardium, especially in the wall of the left ventricle, were small white areas about 0.1 to 0.2 cm. in diameter. The largest area, 0.2 cm. in diameter, near the mitral orifice, gave a good growth of streptococci on culture. Cultures from the heart's blood were positive for streptococci.

Examination of the brain showed distention of the pial vessels. Smears and cultures from the cortex showed streptococci in abundance.

A series of agglutination tests was carried out, by using a suspension of the organism, together with blood serum or cerebrospinal fluid from eight patients with active chorea. No positive results were obtained.

COMMENT

It is difficult to draw any positive conclusions from the results of our work as to the part which bacteria play in the etiology of chorea. In view of the fact that the diphtheroid bacillus isolated from the first patient was nonpathogenic for rabbits, it seems very improbable that it played any part in the etiology of the chorea in this instance. It seems probable that the cocci which developed in the initial cultures from the third and fourth patients were the same as those which were cultivated in the fifth. There is, however, absolutely no proof that this is so; it is merely a supposition. The diplococcus found in the blood smears from the second patient was evidently a different organism. The fact that the streptococcus obtained from the fifth patient caused lesions in the endocardium and joints of rabbits makes it very probable that it was the cause of the endocarditis in the child. The fact that it caused lesions in the brain and meninges of rabbits, similar to those found in the brain and meninges of fatal cases of chorea, suggests that it was also the cause of the chorea in the child. Further than this it is not safe to go. It must also be remembered that there was a local focus of infection in all the cases in which cocci were found in the blood, and that the microorganisms might have been derived from this focus and have had no etiologic connection with the chorea. The absence of organisms in the cerebrospinal fluid in all of the cases in which it was examined is also an argument against the bacterial origin of chorea, because it would seem reasonable to suppose that in a disease in which lesions are located in the nervous system the causative organism would be more constantly present and more abundant in the cere-

brospinal fluid than in the blood. The absence of organisms in the cerebrospinal fluid and in the blood of most of the patients in this series may be explained, however, by the fact that the majority of the cases were mild or only moderately severe in type. It is also possible that the failure to detect organisms more often, either in smears or cultures from the blood, may have been due to the fact that they are only temporarily present in the blood stream and tend to locate themselves in the meninges, endocardium or joints. If this is so, the opportunity of securing a positive culture from the blood is small, even if repeated invasions of the blood occur.

The conclusion seems justified, therefore, both from the study of the literature and from our own work, that while there is much which points to a microorganism or a group of organisms as the cause of chorea, the bacterial origin of chorea has not yet been proved.

THE CEREBROSPINAL FLUID IN CHOREA

Most of the studies of the cerebrospinal fluid in chorea have been made by French observers. The fluid was studied and the cells counted in most instances in order to prove or disprove the organic nature of chorea, a discussion of which was going on at the time. Dupré and Camus²⁴ found a very distinct lymphocytosis in the cerebrospinal fluid obtained by lumbar puncture from a boy of 18 years, ill with a very severe chorea. Babonneix²⁵ found a lymphocytosis in two of five cases. Sicard²⁶ is said to have found a distinct lymphocytosis in a severe febrile case, which was still present after six weeks. Thomas and Tinel²⁷ found a distinct lymphocytosis in a girl of 13, ill three months with chorea. They²⁸ found a similar condition in two of four other patients examined a few months later. Claude²⁹ found a lymphocytosis of six or eight cells to a field in one of two children of 18 years after illness of four months. Gatow-Gatovski³⁰ did lumbar puncture in seven cases and found a distinct lymphocytosis in one and hypertension in one.

Richardière, Lemaire and Sourdel³¹ found a lymphocytosis in twelve of fourteen cases and hypertension in ten. The symptoms were relieved somewhat by lumbar puncture in three cases. The fluid was centrifugalized and the drop at the bottom of the tube examined with an oil immersion lens. The decision as to the presence or absence of

24. Dupré and Camus: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1904, xxi, 361.

25. Babonneix: *Traité des maladies de l'enfance d'Hutinel*, p. 745.

26. Quoted by several authors, reference not given.

27. Thomas and Tinel: *Rev. neurol.*, 1909, xvii, 638.

28. Thomas and Tinel: *Rev. neurol.*, 1909, xvii, 1060.

29. Claude: *Rev. neurol.*, 1909, xvii, 931.

30. Gatow-Gatovski: *Thèse de Paris*, 1910, p. 386.

31. Richardière, Lemaire and Sourdel: *Ann. de méd. et chir. inf.*, 1911, xv, 276.

a lymphocytosis depended on the number of cells seen per field. This is the method which was apparently used by all the French observers and does not seem at all exact. They conclude that there is almost constantly a lymphocytosis in the cerebrospinal fluid in acute chorea and that it is the most constant of the signs of an organic lesion yet discovered.

Negative results were obtained by many other observers. It is probable, moreover, that a much larger proportion of the positive than of the negative results have been recorded.

Deléarde and Valetti³² found a lymphocytosis in one of ten cases. There was hypertension in some cases. They think that this is of no diagnostic importance, because hypertension is present in many diseased conditions. Prolonged vomiting followed the punctures in several cases.

Comby⁹ found 12 lymphocytes per c.mm. in one of seven cases. There was no excess in the others.

Original Investigations.—Lumbar puncture was done twenty times in nineteen of our cases. The cerebrospinal fluid was perfectly clear in every instance. The pressure was apparently slightly increased in one instance. It was normal in all the others. A fibrin clot was never formed. The number of cells per cubic centimeter was counted in ten cases, and was, respectively, 2, 5, 7, 8, 10, 10, 10, 18, 24 and 25. There was, therefore, a slight increase in the number of cells in three of the ten cases, or 30 per cent. The cells were all mononuclear in every case.

Lumbar puncture had no noticeable effect on the symptoms, either for better or worse, at the time or later, in any instance.

CONCLUSIONS

Our investigations show that syphilis plays no direct part in the etiology of chorea. Our results suggest that a microorganism or a group of microorganisms may be the cause of chorea. They seem to show that if chorea is caused by a microorganism, the source of infection is ordinarily in the tonsils or teeth. They tend to confirm the belief that there is an intimate relation between chorea, rheumatism and endocarditis.

32. Deléarde and Valette: Arch. de méd. d. enfants, 1913, xvi, 481.

THE CURVED LINES OF SUCTION *

MICHIO KASAHARA, M.D.

JAPAN

With regard to the mechanism of an infant's suction, many problems still remain unsolved. According to the studies by Burdach,¹ Funke,¹ Meissner,² Allix³ and Herz,⁴ the negative pressure in an infant's oral cavity which is necessary for sucking milk is chiefly made by inspiratory action, while Biedert⁵ and Vierordt⁶ attribute it to the enlargement of the vertical diameter of the oral cavity, the lower jawbone being drawn downward. After detailed researches, Auerbach⁷ in 1888 made a new discovery in connection with the physiology of suction in general. He divided the action into two kinds: (1) suction by inspiration, and (2) suction by the mouth, or the tongue.

Suction by inspiration is made by adults, and the negative pressure in the mouth necessary for suction is chiefly caused by inspiratory action; while suction by the mouth is made by infants, and the negative pressure in the mouth is chiefly due to the vertical diameter of the oral cavity being enlarged, because the lower jawbone is drawn downward. Auerbach's opinion is generally accepted now as true, that suction by the mouth does not change to suction by inspiration till an infant is two or three years old. Basch,⁸ Pfaundler⁹ and Süsswein,¹⁰ who made further studies on the subject in later years, were of the same opinion, that is, that the negative pressure in the mouth when an infant sucks milk is chiefly attributable to the draw of the lower jawbone, and suction by inspiration is made by an adult, but not by an infant.

In respect to the change of the form of the tongue when milk is sucked and the effect which the change or the movements of the tongue has on the mechanism of suction, many authors seem to entertain different opinions. Auerbach says that the change in the

* Submitted for publication March 28, 1916.

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1. Burdach, cited from Escherich: München med. Wehnschr., 1888, xli, 687.

2. Meissner: Lehrbuch der Kinderheilkunde.

3. Allix: Etude sur la physiologie, 1867, Paris.

4. Herz: Jahrb. f. Kinderh., 1865, vii, 46.

5. Biedert: Deutsch. Arch. f. klin. Med., 1875, xviii, 115.

6. Vierordt: In Gerhards Handbuch, I, 112.

7. Auerbach: Du-Bois Reymonds Arch. f. Physiol., 1888, 59.

8. Basch: Arch. f. Gynäk., 1893, xlix, 15.

9. Pfaundler: Verhandlung d. Gesellsch. f. Kinderh., 1899.

10. Süsswein: Arch. f. Kinderh., 1904, xl, 68.

form of the tongue does not have much influence in the mechanism of suction; while Basch and Pfaundler attach importance to this change in the shape of the tongue in the suction of milk, as being a prominent feature of the mechanism. Basch observes that the suction of milk is accomplished not wholly by the negative pressure in an infant's mouth, but the act is assisted by the pressure of the nipple effected by the closure of the jawbones.

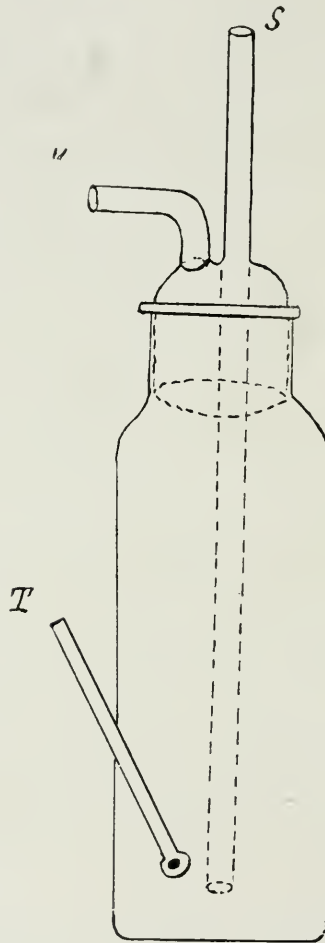


Fig. 1.—Drawing showing apparatus used as a nursing bottle in obtaining the records of the negative pressure of suction.

It is a generally known fact that infants possess certain anatomic features which nature has provided for performing the act of sucking milk. The gingivale and sucking-bolster (Bichat's bolster) might be mentioned, but it is not my intention to deal with them in detail now.

As regards an infant's suction, Herz,⁴ Biedert,⁵ Pfaundler,⁹ Cramer,¹¹ Basch,⁸ and Barth¹² studied it in their respective methods, but they simply measured, by means of some arrangements, the negative pressure in an infant's oral cavity necessary for the suction of milk.

I made, however, the following experiment in order to register by curved lines the change of the pressure:

Figure 1 shows a nursing bottle of from 100 to 150 c.c. capacity, which I used in my experiment. The glass tube *S* in the bottle, about 5 mm. in diameter, is connected at the upper end by means of a rubber tube with a nipple, such as is in common use. The glass tube *K*, 5 mm. in diameter, is connected with Marey's tambour by means of a rubber tube. *T* is a thermometer to show the temperature of the milk in the bottle.

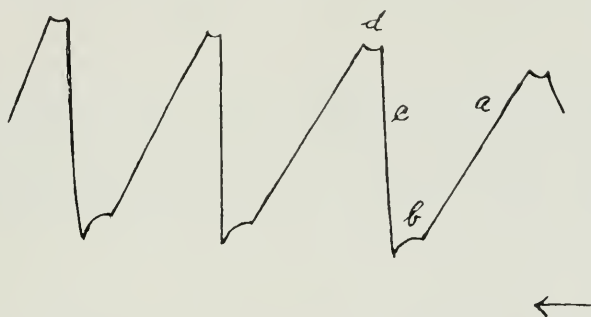


Fig. 2.—Curved lines of suction registered by infants in good health.

Milk of a certain temperature was put into the nursing bottle, and an infant was permitted to suck at the nipple with the result that every change of pressure in the oral cavity was given to Marey's tambour, and was registered on the blackened paper closely-attached to the kymograph. Jaquet's watch was used to measure the speed of the registering tube which was turning around. The child was put on its mother's knee, a little aslant in posture, with the kymograph back of the mother. The kymograph should be as noiseless as can be obtained. By this experiment were obtained the curved lines which I call the curved lines of suction.

I examined seventy-five infants in good health under artificial feeding and Figure 2 is a schema of the curved lines of suction registered by these infants. The milk in the nursing bottle had the temperature of 37 C., or thereabouts. The curved lines thus obtained can

11. Cramer: *Zur Mechanik u. Physiologie d. Nahrungsaufnahme d. Neugeborenen.*

12. Barth: *Ztschr. f. Kinderh.*, 1914, x, 129.

be subdivided into four parts: (1) the descending part (*a*); (2) a small elevation (*b*); (3) the ascending part (*c*); (4) the notch (*d*).

1. The descending part of the curve represents the downward movement of the lower jawbone, the oral cavity being extended in the vertical diameter.

2. The small elevation is due to the pressure on the nipple attached to the rubber tube.

3. The ascending part of the curve may be attributed to the running down of the milk which has been taken into the mouth.

4. The notch is a concave curve caused by the swallowing.

The curved lines of suction above mentioned are made by most infants (Figs. 3 to 9), yet the small elevation is not always given clearly (Figs. 10 and 11). The notch varies with different postures of an infant, being clearer when the child lies down than when it sits.

Rarely the curved lines shown in Figures 12 to 14 are made by a healthy infant. In this case the ratio of the time required for sucking the milk to that for swallowing it is 2:1. These lines are so rare that only three of the seventy-five healthy infants made them in my experiments.

Healthy infants over a week old are always regular in making the curved lines of suction, and never discontinue to do so, while a newborn infant sometimes discontinues them for physiologic reasons (Figs. 15 to 18). In that case, as the figures show, a certain pause is made after regular curved lines of suction, but the lines are resumed after the pause. This physiologic pause, however, is to be seen no more when an infant is a week old.

An infant fed by its maternal breast and unaccustomed to sucking milk from the nipple attached to a rubber pipe makes irregular curved lines of suction at first (Figs. 19 to 22), but as soon as it is accustomed to that way of suction it will make regular lines.

I gave healthy infants milk of various degrees of temperature in order to determine, by studying the lines thus obtained, what relations there are between the curved lines of suction and the temperature of the milk.

The conclusion I arrived at was, as Figures 23 to 27 show, that the curved lines of suction are irregular when milk is below 20 C. or above 40 C, but regular and never discontinued when the temperature is between 30 and 40 C.

The curved lines of suction made by infants of premature birth and in atrophy are always remarkably irregular and often discontinued (Figs. 28 to 38), but become regular in proportion to the increase of the weight of the infant and the improvement of nutrition.

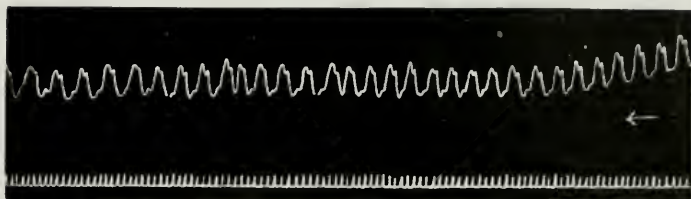


Fig. 3.—O. H., healthy infant, aged 2 months (time, one-fifth second).

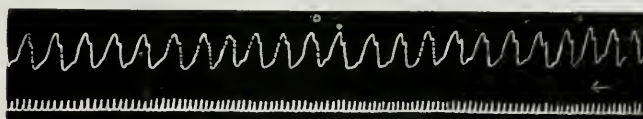


Fig. 4.—J. S., healthy infant, aged 5 months (time, one-fifth second).

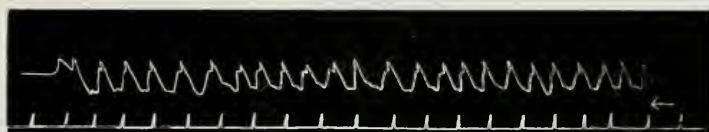


Fig. 5.—M. O., healthy infant, aged 6 months (time, one second).

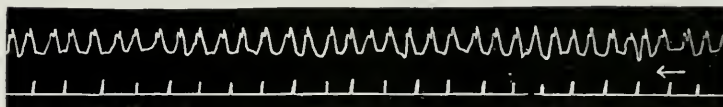


Fig. 6.—K. M., healthy infant, aged 1 month (time, one second).

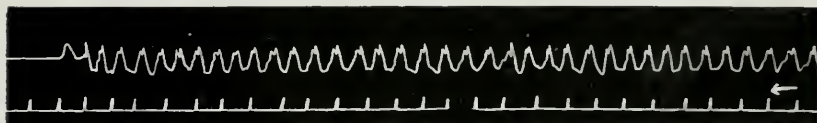


Fig. 7.—K. Y., healthy infant, aged 3 weeks (time, one second).

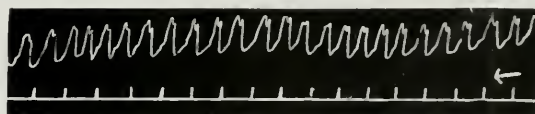


Fig. 8.—A. O., healthy infant, aged 1 week (time, one second).

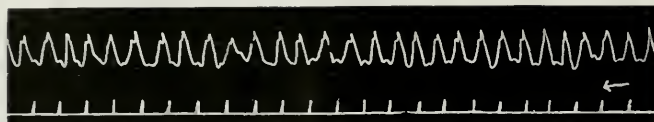


Fig. 9.—K. K., healthy infant, aged 2 weeks (time, one second).

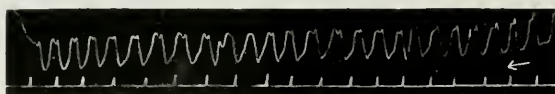


Fig. 10.—G. I., healthy infant, aged 1½ months (time, one second).



Fig. 11.—K. T., healthy infant, aged 5 months (time, one second).



Fig. 12.—K. T., healthy infant, aged 6½ months (time, one-fifth second).

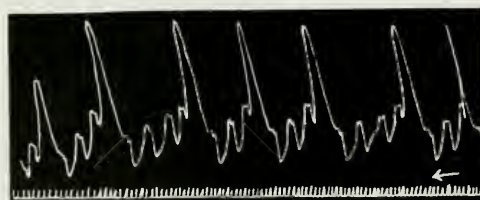


Fig. 13.—S. T., healthy infant, aged 3 months (time, one-fifth second).

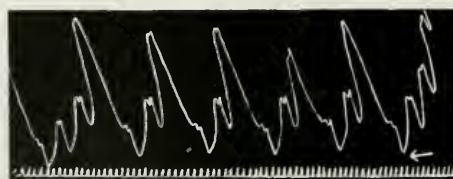


Fig. 14.—J. U., healthy infant, aged 2 months (time, one-fifth second).

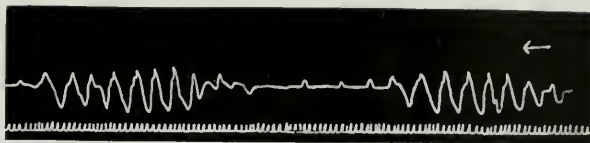


Fig. 15.—I. K., healthy newborn baby (time, one-fifth second).

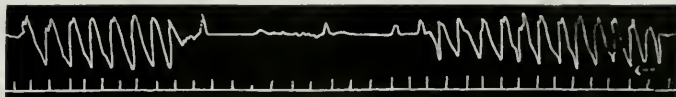


Fig. 16.—K. U., healthy newborn baby (time, one second).

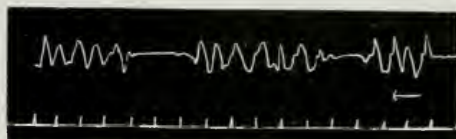


Fig. 17.—M. G., healthy newborn baby (time, one second).

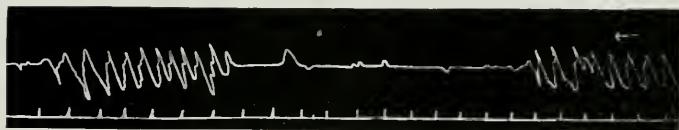


Fig. 18.—K. S., healthy newborn baby (time, one second).

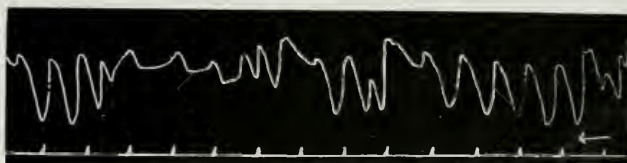


Fig. 19.—K. T., healthy breast-fed infant, aged 1 month (time, one second).

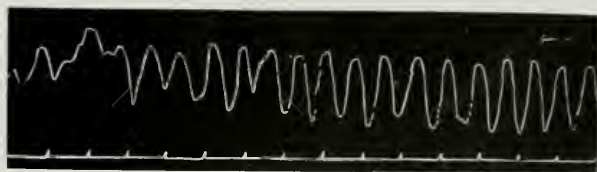


Fig. 20.—T. Y., healthy breast-fed infant, aged 3 months (time, one second).

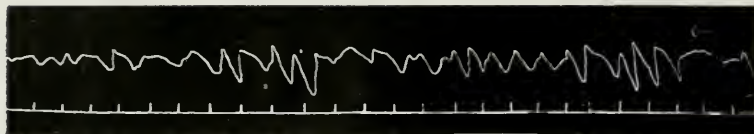


Fig. 21.—K. K., healthy breast-fed infant, aged 4 months (time, one second).

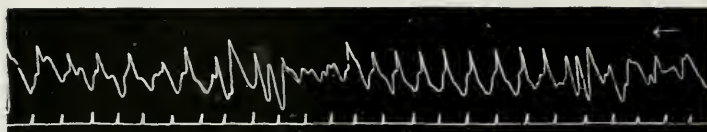


Fig. 22.—T. T., healthy breast-fed infant, aged 6 months (time, one second).

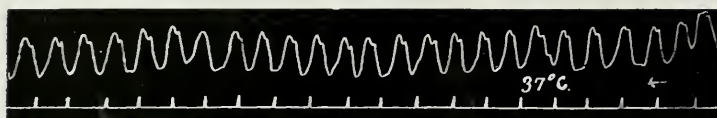


Fig. 23.—M. K., healthy infant, aged 3 months; the temperature of the milk 37 C. (time, one second).

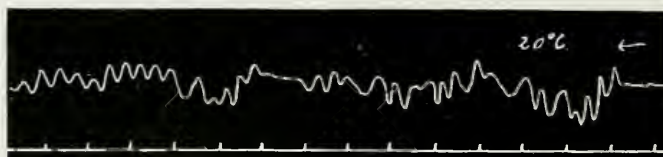


Fig. 24.—M. K. The temperature of the milk 20 C. (time, one second).

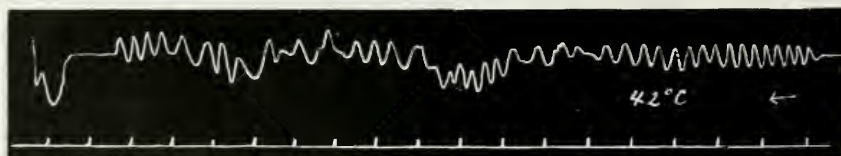


Fig. 25.—M. K. The temperature of the milk 42 C. (time, one second).



Fig. 26.—M. K. The temperature of the milk 40 C. (time, one second).

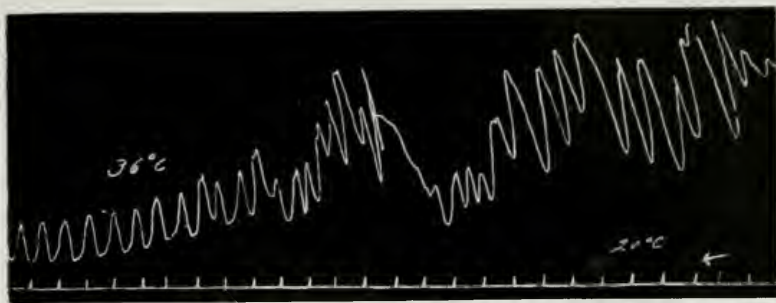


Fig. 27.—H. K., healthy infant, aged 2 months (time, one second).

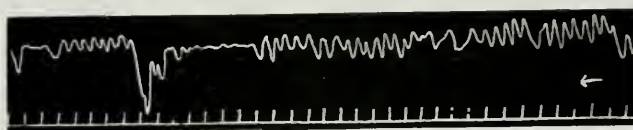


Fig. 28.—T. Y., infant of premature birth (time, one second).



Fig. 29.—O. U., infant of premature birth (time, one second).

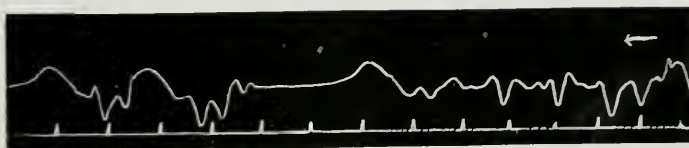


Fig. 30.—K. K., infant of premature birth (time, one second).



Fig. 31.—O. O., infant of premature birth (time, one second).

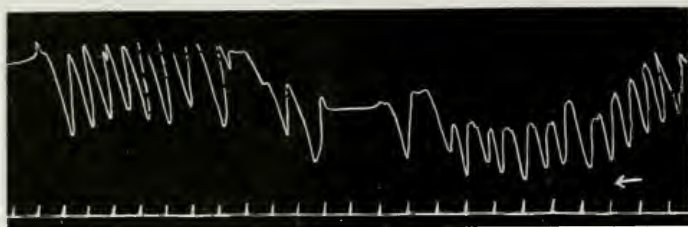


Fig. 32.—U. K., aged 3 months, weight 3.15 kg. (time, one second).

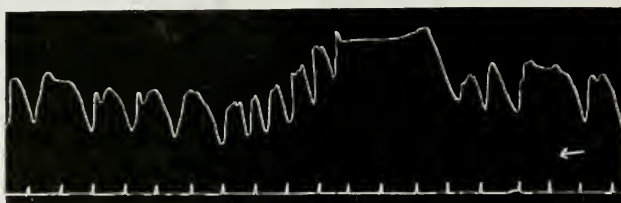


Fig. 33.—T. T., aged 2 months, weight, 2.5 kg. (time, one second).

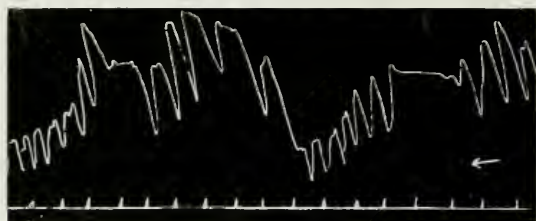


Fig. 34.—K. M., aged 3 weeks, weight, 2 kg. (time, one second).

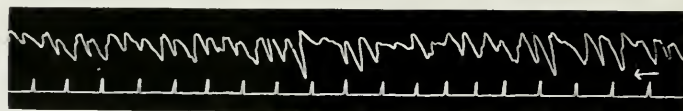


Fig. 35.—K. M., aged 5 months, weight, 3.1 kg. (time, one second).

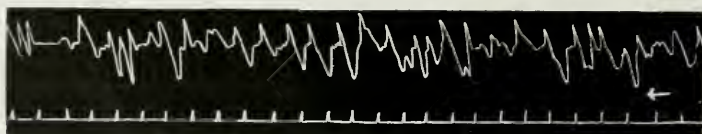


Fig. 36.—S. Y., aged 6 months, weight, 3.8 kg. (time, one second).

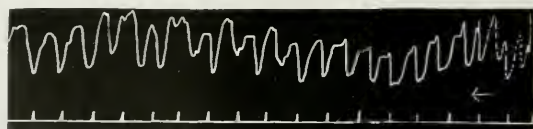


Fig. 37.—M. S., aged 4 months, weight, 3.95 kg. (time, one second).

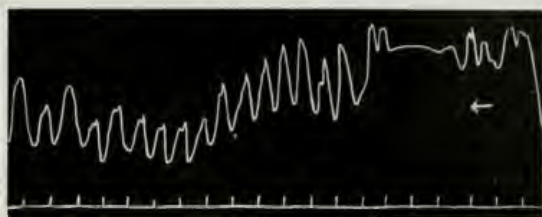


Fig. 38.—T. H., aged 1 month, weight, 2.01 kg. (time, one second).

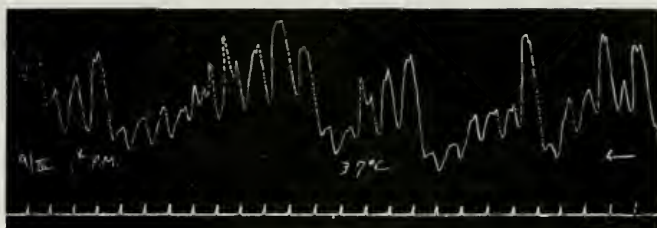


Fig. 39.—H. O., aged 5 months, with thrush (time, one second).

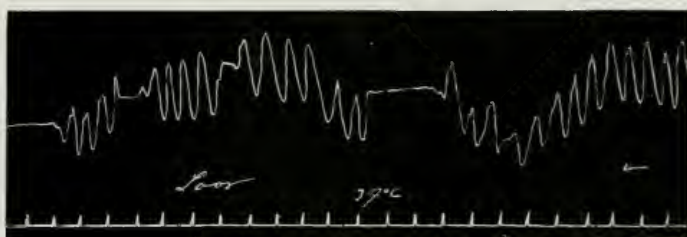


Fig. 40.—M. S., aged 2 months, with thrush (time, one second).

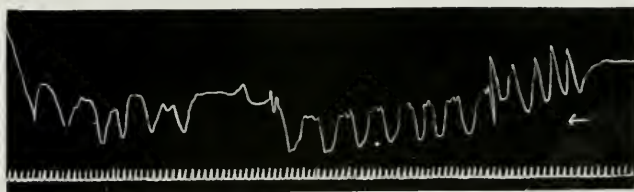


Fig. 41.—J. M., aged 4 months, with aphthae (time, one-fifth second).



Fig. 42.—M. N., aged 2 months, with aphthae (time, one second).

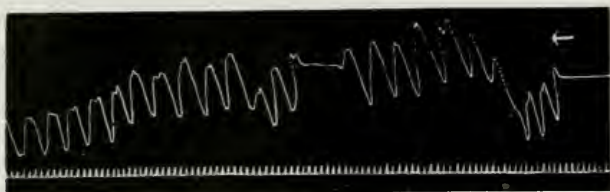


Fig. 43.—K. U., aged 2 months, with aphthae (time, one-fifth second).

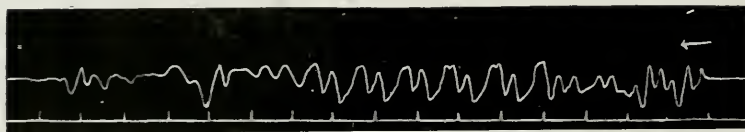


Fig. 44.—I. H., aged 3 weeks, with nasal catarrh (time, one second).

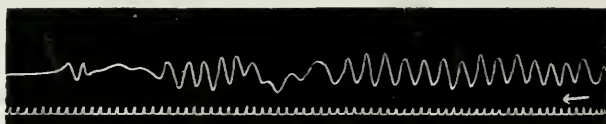


Fig. 45.—M. I., aged 3 months, with nasal catarrh (time, one-fifth second).

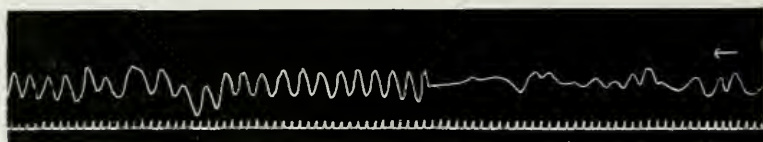


Fig. 46.—S. I., aged 5 months, with nasal catarrh (time, one-fifth second).

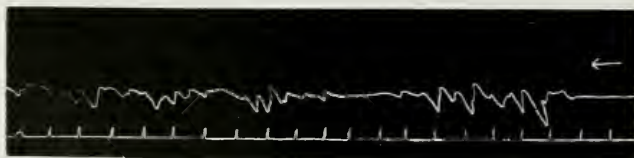


Fig. 47.—K. T., aged 4 months, with nasal catarrh (time, one second).

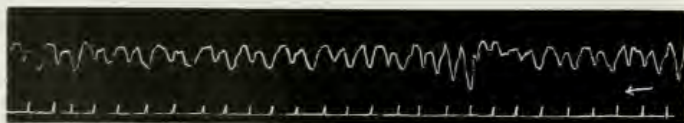


Fig. 48.—T. N., aged 3 months, with acute otitis (time, one second).



Fig. 49.—M. O., aged 2½ months, with acute otitis (time, one second).



Fig. 50.—K. K., aged 6 months, with acute otitis (time, one second).

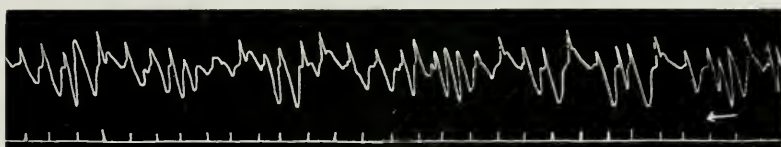


Fig. 51.—M. G., aged 1 month, with hereditary syphilis (time, one second).

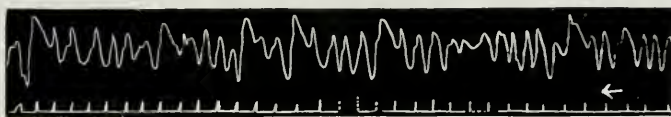


Fig. 52.—K. K., aged 2 months, with hereditary syphilis (time, one second).

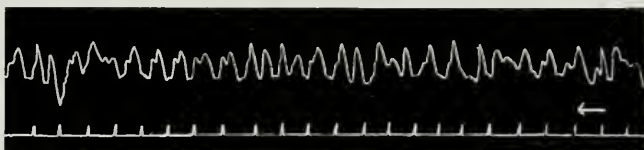


Fig. 53.—M. T., aged 3 months, with hereditary syphilis (time, one second).

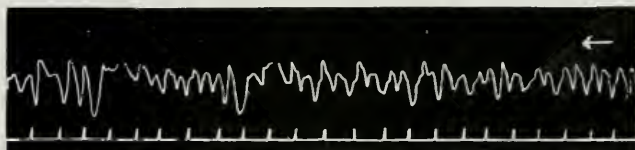


Fig. 54.—H. T., aged 1 month, with hereditary syphilis (time, one second).

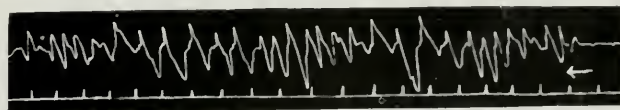


Fig. 55.—S. T., aged 3 months, with hereditary syphilis (time, one second).

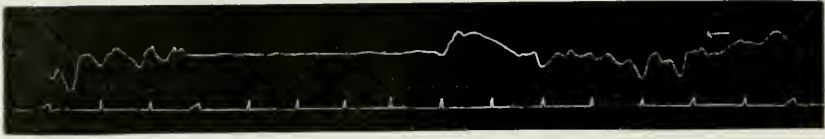


Fig. 56.—I. K., aged 3 months, idiocy (time, one second).



Fig. 57.—M. N., aged 5 months, idiocy (time, one second).



Fig. 58.—O. K., aged 6 months, idiocy (time, one second).



Fig. 59.—K. H., aged 5 months, idiocy (time, one second).

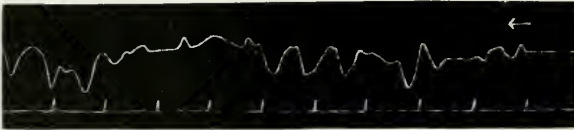


Fig. 60.—O. I., aged 5 months, with myxedema (time, one second).

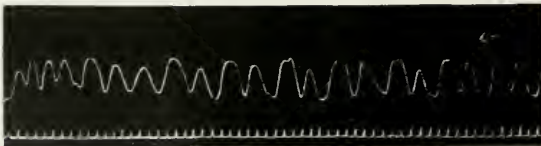


Fig. 61.—O. I., after thyro-iodin treatment (time, one-fifth second).

Certain diseases in the mouth, such as thrush (Figs. 39 and 40) and aphthae (Figs. 41 to 43); diseases of the respiratory organs, such as nasal catarrh (Figs. 44 to 47); diseases of the ears, such as acute otitis (Figs. 48 to 50), all make the curved lines of suction irregular, but they become regular again as soon as the diseases are cured. An infant who is suffering from hereditary syphilis and whose nose is obstructed makes the most irregular curved lines of suction (Figs. 51 to 55).

It is an interesting fact to notice that idiots always make irregular curved lines of suction, probably because there are disorders in the coordination of muscles, which is necessary for suction (Figs. 56 to 59). In an infant who was suffering from myxedema I saw that the curved lines of suction were irregular (Fig. 60), but as soon as the psychical development improved after the thyro-iodin treatment was kept up, the lines became gradually regular (Fig. 61).

SUMMARY

1. The curved lines of suction made by infants in good health are always regular and never discontinued.
2. When an infant in good health sucks and swallows milk the time ratio of the two acts is 1 to 1, or rarely, 2 to 1.
3. In the case of a newborn baby, the curved lines of suction are discontinued now and then for physiologic reasons. In this case there is a certain pause between regular curved lines of suction.
4. Infants of premature birth or in atrophy make very irregular curved lines of suction, and often discontinue them, but the lines gradually become regular again when the state of nutrition improved.
5. Certain diseases of the mouth, nasal catarrh, and acute otitis, etc., make the curved lines of suction irregular, but they become regular again when the diseases are cured.
6. The curved lines of suction will become irregular when the temperature of milk is below 20 C. or above 40 C.
7. Idiots are unskilful in suction, and so the curved lines are always irregular.

I wish to take this opportunity to thank Prof. I. Hirai for his valuable suggestions in connection with this work.

Kyoto, Japan.

PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE ON THE METABOLISM OF NORMAL INFANTS.*

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BALTIMORE

Full reviews of the literature on the metabolism of infants under both normal and pathologic conditions appear in the recent textbooks of Langstein and Meyer,¹ and of Morse and Talbot.² Niemann³ and Benedict and Talbot⁴ present critical reviews of the literature on the respiratory exchange of infants, and Hellesen⁵ reviews the entire subject of normal infant metabolism.

TOTAL ENERGY METABOLISM OF THE NEWLY BORN

Hasselbalch,⁶ whose work except in Danish, has only recently become available, found that the amount of the infant's metabolism is to a very large extent dependent on muscular contractions, violent crying causing an increase in the total heat production of more than 100 per cent. At 32 C. and with the minimum muscular work the metabolism per kilogram of the newly born infant is hardly greater than that of the adult at complete rest. He observed a total heat production of as low as 30 calories per kilogram, calculated on the basis of twenty-four hours; it was seldom as great as 40 calories. Hasselbalch concluded from the high respiratory quotients observed with infants during the first hours of life that the metabolism depends chiefly and at times entirely on the oxidization of carbohydrates. The well-nourished infant, born at full term, possesses a store of carbohydrate (glycogen) in his organs, which is spent in the course of a few hours. As premature infants also possess a store of glycogen and show an exclusive metabolism of carbohydrates just after birth, Hasselbalch states that there is every reason to suppose that the metabolism of the normal, well-nourished human fetus depends on the oxidization of carbohydrates.

* Submitted for publication May 31, 1916.

1. Langstein and Meyer: *Säuglings Ernährung und Säuglingsstoffwechsel*, Ed. 2, 1914, Wiesbaden.

2. Morse and Talbot: *Diseases of Nutrition and Infant Feeding*, 1915, New York.

3. Niemann: *Ergebn. d. inn. Med. u. Kinderh.*, 1913, xi, 32.

4. Benedict and Talbot: *Pub. Carnegie Inst., Wash.*, 1914, No. 201; *ibid.*, 1915, No. 233; *AM. JOUR. DIS. CHILD.*, 1914, viii, 1.

5. Hellesen: *Nord. med. Ark.*, 1915, xlviii, 1, 42.

6. Hasselbalch, *Bibliot. f. Laeger*, 1904, viii, 219, translated and appearing in publication No. 233, *Carnegie Institute of Washington*, 1915.

When the infant is fed with breast milk, the respiratory quotient shows that carbohydrate is the element most quickly utilized; it is completely metabolized within about one and a half hours after the meal. When the carbohydrate has been used up, as shown by a drop in the respiratory quotient, infants usually show evidences of hunger, such as vigorous sucking of the fingers and crying. When glucose is fed, the respiratory quotient gives no evidence of oxidization of carbohydrate until one-half hour after the feeding; the oxidization is, however, apparently completed within two and one half hours.

Benedict and Talbot⁷ discuss critically Hasselbalch's work and suggest the presence of errors in his technic. They were unable to confirm Hasselbalch's observation that shortly after birth carbohydrates are exclusively utilized. Their results indicate that not more than two thirds of the total heat production results from the oxidization of carbohydrates. During the first day of life the average respiratory quotient corresponds to a metabolism in which only about one third of the energy comes from carbohydrate and two thirds from fat. The respiratory quotient is practically the same as that occurring during the first twenty-four hours of fasting in the normal human adult. After the first feeding of milk Benedict and Talbot observed very constantly a rise in the respiratory quotient, indicating the utilization of carbohydrate. Contrary to the findings of Hasselbalch, they found that the respiratory quotient was independent of the body weight, small infants having the same respiratory quotients as larger ones.

Benedict and Talbot⁴ discuss critically Hasselbach's work and of life the total energy exchange during periods of rest varies from 32 to 52 calories per kilogram of body weight per twenty-four hours, with an average of 42 calories per kilogram. Approximately half of the infants studied gave energy quotients falling within 10 per cent. of this average value. The basal heat production, calculated on the basis of square meters of body surface, as determined by Lissauer's formula, was 612 calories. Two thirds of the infants studied showed values within 10 per cent. of this average. The extreme variations were from 459 to 732 calories per square meter of body surface per twenty-four hours. The metabolism during the first twenty-four hours of life is somewhat less than on subsequent days. Benedict and Talbot deny any close relationship between total metabolism and either the body surface or the body weight in the newly born. They explain the wide variations observed when the total metabolism is calculated in terms of square meters of body surface as due to a failure to consider the length of the child in the calculations. All formulas previously suggested for the determination of body surface, which ascribe the same surface area and therefore the same metabolism to a thin and a fat child of the same weight are necessarily incorrect. Benedict and

Talbot found that the energy exchange per square meter of surface bears a more or less definite relationship to body length. They found the total heat production to be from 11.9 to 13.4 calories per square meter of body surface per centimeter of length per twenty-four hours, the average being 12.65 calories. On this basis they suggest a formula for the calculation of the heat production of infants during the first week of life. The formula is as follows: Length in cm. $\times 12.65 \times 10.3 \times \sqrt[3]{Wt^2}$.

They give tables for the computation of the total caloric output for any infant on the basis of this formula. Using this formula in the study of the heat production of 105 newly born infants, they found that observed and calculated values for the total metabolism agreed within 6 per cent. in nearly every instance. The total metabolism calculated in this way is the basal, starving, resting metabolism. In any infant during twenty-four hours the actual requirement is greater, as in this computation no allowance is made for growth, for activity or for unabsorbed food. Benedict and Talbot, in accordance with previous observers, have noted a very marked influence of muscular activity on the total heat production. During violent crying they observed an increase as high as 211 per cent. The average increase in metabolism due to moderate activity was 65 per cent. The total metabolism is also increased by exposure to a low temperature. These authors suggest that on the basis of the whole twenty-four hours, 30 per cent. should be added to the basal heat production to allow for activity and that 10 per cent. should be added for the loss of food due to non-absorption. In the light of these considerations they calculate the average daily energy requirement during the first week of life, including both the maintenance metabolism and the metabolism due to activity, to be approximately 62 calories per kilogram per twenty-four hours. This estimate allows no provision for growth.

TOTAL ENERGY METABOLISM OF OLDER INFANTS

Benedict and Talbot⁴ have also studied the heat production of a group of thirty-seven infants varying in age from 19 days to 18 months. The infants were all approximately normal, although a number were below the average in weight for the age. They found the average basal resting heat production during the postabsorptive stage, that is, from one to one and one half hours after a feeding, to be 65 calories per kilogram of body weight. The extreme values observed were 44 and 88 calories per kilogram, respectively. These authors state that, "aside from a slight tendency for the total metabolism to be larger with increasing weight, no regular relationship exists with infants between the total heat production and the body weight, regardless of whether the body weight was actually found, computed from statis-

tics of average values for normal infants, or was the expected body weight based on the birth weight." Calculating the body surface by means of the several formulas of Meeh, Lissauer, and of Howland, they find the heat production to vary from 656 to 1,367 calories per square meter of body surface. They state on the basis of these findings that no constancy in relationship exists between body surface and total metabolism, at any rate when the body surface is computed by means of any of the formulas so far devised. They conclude that the extent of metabolism is determined neither by weight nor by surface area, but by the mass of active protoplasmic tissue, as suggested by Howland. They consider it likely that with normal infants of varying weight the active protoplasmic mass varies directly with the age. Excessive or deficient adipose tissue, representing relatively inactive protoplasmic mass, may cause a failure of agreement between the heat production calculated from the surface area and that actually measured. The apparent relationship that has been previously observed between the heat output and the body surface with normal or nearly normal individuals is explained on the basis that with such individuals a simple relationship exists between the body surface, blood volume, body weight, and the mass of active protoplasmic tissue. Benedict and Talbot determined further that in the infant the specific dynamic action of food is relatively slight, since they found practically the same heat production one hour after feeding and twenty-one hours after. The pulse rate, they find, is roughly proportional to the total metabolism as far as the same infant is concerned; but a difference in the pulse rate of any two infants does not necessarily indicate a proportional difference in metabolism, even when the infants are of the same age and weight. They do not believe the increased metabolism noted with increased pulse rate is due exclusively to the mere mechanical work of the circulation, but that the pulse rate is rather to be considered as an index of muscle and general tonus in the body.

Murlin and Hoobler⁸ studied the total energy metabolism of ten hospital children ranging in age from two to twelve months and in nutritive condition from extreme marasmus to excessive weight. None of the children were acutely ill. The subjects were fed immediately before the observation; and slept a large part of the time they were in the calorimeter. The average heat production for the sleeping periods was 65 calories per kilogram of body weight, calculated on the basis of twenty-four hours. The extreme variations were from 60 to 84 calories, the highest heat production per kilogram being observed in the case of atrophic children and the lowest in the case of normal or overweight children. The average heat production calculated on the basis of surface area (Meeh's formula) was 950 calories per square

8. Murlin and Hoobler: *AM. JOUR. DIS. CHILD.*, 1915, ix, 81.

meter. The average deviation from the mean on the basis of weight for all the children studied was 12.1 per cent., on the basis of surface area 11 per cent. For the infants under 6 months the deviation on the basis of weight was less than on the basis of surface area. Murlin and Hoobler conclude that, if one takes into account the possible variations in the specific dynamic action of the food, the results must be taken as confirmatory of Rubner's law of surface area; they do not feel, however, that there is a sufficient reason for estimating the heat production on the basis of surface area rather than on the basis of weight. The pulse rate of infants of different ages, they found, could not be taken as a criterion of the extent of metabolism.

Niemann⁸ observed a very constant heat production during the first year of life of from 900 to 1,000 calories per square meter of calculated body surface. Hellesen⁵ found the resting heat production of a normal 5 months old infant to be 68 calories per kilogram of body weight, or 1,076 calories per square meter of calculated body surface. When a portion of the carbohydrate of the diet was replaced by an isodynamic amount of fat, the heat production increased 8.3 per cent. Schlossman,⁹ on the other hand, observed an increase of 15 per cent. in the heat production of an infant as the result of a substitution of an isodynamic quantity of carbohydrate in place of part of the fat of the diet.

Frank and Niemann¹⁰ found the total carbon dioxide production to be approximately 10 per cent. greater with artificial feeding than with breast feeding. They attributed this difference to the specific dynamic action of the proportionately larger amount of protein in the artificial mixture. Samelson,¹¹ however, determined the total caloric intake of normal twins of the same size and state of nutrition, the one being fed on artificial mixtures and the other on breast milk, and found a somewhat lower intake in the case of the artificially fed infant. The infants thrived equally well. The total intake, as determined by analysis of the food, was never greater than 100 calories per kilogram with either infant. Premature infants, however, fed on mixed breast milk consumed from 115 to 140 calories per kilogram.

Pritchard¹² states that the energy requirement of infants is exceedingly dependent on the character of the clothing and also on humidity and ventilation. The amount of time that the infant is allowed daily for the free use of the limbs also exerts a distinct influence on the total energy requirement. An infant warmly clothed and allowed very little exercise has a lower food requirement.

9. Schlossmann: München. med. Wchnschr., 1913, ix, 285.

10. Frank, K., and Niemann: Charité-Ann., 1913, xxxvii, 94.

11. Samelson: Habilitationsschrift, Strassburg. Springer, Berlin, 1913.

12. Pritchard, E.: Brit. Jour. Child. Dis., 1914, xi, 49.

METABOLISM DURING STARVATION

Schlossmann¹³ and Schlossmann and Murschhauser¹⁴ determined the effects of starvation on the metabolism of infants. Healthy infants were starved for from seventeen to seventy-two hours. They received water, salt and saccharin at the regular feeding intervals and seemed to experience no discomfort. Infants previously fed on artificial mixtures at first gained slightly in weight, then began to lose. There was, at the beginning of the fast, a decreased nitrogen elimination, which subsequently increased. Infants previously fed on breast milk, however, showed, from the beginning, an increased nitrogen elimination, but the total amount during the period of fasting was always less than in the case of the artificially fed infants. The feeding of a small amount of lactose invariably led to a marked diminution in the nitrogen output. The blood sugar content remained normal until near the end of the fasting period, when a slight fall occurred. Acetone and diacetic and beta-oxybutyric acid excretion began after twelve hours of starvation. The quantities excreted increased slowly at first, but later the excretion became as great as that of an adult fasting for the same length of time. The beta-oxybutyric acid excretion was always greater than the acetone excretion, but ran parallel to the latter. In every instance the administration of as much as 70 gm. of lactose per day prevented entirely the excretion of acetone bodies. Elimination of lactose from the diet resulted in a prompt return of the acetonuria. During the fasting periods the carbon dioxide production fell approximately 10 per cent. The total metabolism, calculated in terms of the different foodstuffs, showed that at the end of forty-eight hours fasting 1.74 gm. of protein, 2.95 gm. of carbohydrate and 4.47 gm. of fat were metabolized in the course of twenty-four hours. At the end of seventy-two hours the protein metabolism had increased to 2.24 gm., the carbohydrate had remained the same, 2.95 gm., while the fat consumed had fallen to 3.53 gm.. Infants fed on a high carbohydrate diet previous to the fast showed higher respiratory quotients than those fed on a high fat diet. The authors attributed this difference to the greater amount of stored-up glycogen used by the infants previously fed on carbohydrates. The respiratory quotients showed further that fat infants during starvation burned relatively more fat and less carbohydrate than thinner ones.

THE METABOLISM OF CARBOHYDRATES

Porter and Dunn¹⁵ state that the addition of as much as 120 gm. of lactose to the feedings of infants with indigestion in the course of twenty-four hours does not lead to the excretion of a sufficient amount

13. Schlossmann: Vortrag geh. in d. deutsch. ges. f. Kinderh., 1913, ix, 24.

14. Schlossmann and Murschlauser: Biochem. Ztschr., 1913, lvi, 335.
Schlossmann, M.: *ibid.*, 1914, lviii, 483.

15. Porter and Dunn: AM. JOUR. DIS. CHILD., 1915, x, 77.

of sugar in the urine to be determined quantitatively by the usual methods. On the basis of these experiments they urge the more frequent use of fair amounts of sugars in nutritional disorders.

Talbot and Hill¹⁶ determined that the administration of a moderate amount of lactose in the diet increases nitrogen retention, but that large amounts, sufficient to cause loose stools, lead to a negative nitrogen balance. Small amounts of lactose have no effect on fat absorption; larger amounts decrease fat absorption and lead to the production of diarrhea, with acid stools and a negative mineral balance. Weill and Dufourt¹⁷ confirm Talbot and Hill's results as to the effect of lactose on the reaction on the stools. They find, however, that the addition of as much as 25 gm. of glucose to the diet does not serve to make the stools acid. Carneiro¹⁸ found that withdrawal of carbohydrates from the diet leads to a negative nitrogen balance and to a negative ash balance, chlorin being lost to a greater extent than any other ash constituent.

BLOOD SUGAR

Götzky,¹⁹ using the Bang method, found the blood sugar during the first twelve days of life to average 0.085 per cent., at one month 0.095 per cent. and at one year 0.102 per cent. Bass,²⁰ using the Benedict-Lewis method for sugar determination in the blood, found in children from 2 to 14 years of age, sugar contents ranging from 0.072 to 0.113 per cent. These variations are approximately the same as those occurring in adults. Bergmark²¹ reports that the feeding of maltose leads to a higher blood sugar than does the feeding of lactose, but that cane sugar causes a greater increase in blood sugar than either lactose or maltose. He believes that this difference in behavior is due to differences in intermediary metabolism rather than in the rate of absorption, since the increase in carbon dioxid production following the feeding of the different sugars does not run parallel to the increases in the blood sugar.

Schloss and Schroeder²² have identified the reducing substance of the cerebrospinal fluid as glucose. The concentration in the cerebrospinal fluid varies from 0.05 to 0.134 per cent.

CARBOHYDRATE AND WATER METABOLISM

Niemann²³ finds that the addition of 40 to 50 gm. of carbohydrate to the diet of infants either in the form of milk sugar or cereal leads to a great decrease in the daily volume of the urine. Cane sugar, to

16. Talbot and Hill: *AM. JOUR. DIS. CHILD.*, 1914, viii, 218.

17. Weill and Dufourt: *La Nourrisson*, 1914, ii, 65.

18. Carneiro: *Monatsch. f. Kinderh.*, 1913, xii, 333.

19. Götzky: *Ztschr. f. Kinderh.*, 1913, ix, 44.

20. Bass: *AM. JOUR. DIS. CHILD.*, 1915, ix, 77.

21. Bergmark: *Jahrb. f. Kinderh.*, 1914, lxxx, 373.

22. Schloss and Schroeder: *AM. JOUR. DIS. CHILD.*, 1916, xi, 1.

23. Niemann: *Jahrb. f. Kinderh.*, 1915, lxxxii, 21.

the contrary, causes no diminution in the urinary output. Coincident with diminished urinary secretion, an increase in the body weight occurs. No increased water loss occurs by way of the intestinal tract or by the lungs, nor does Niemann consider it likely that there is an appreciable increase in the water loss by the expired air or the perspiration. He believes that a true water retention occurs, due to the carbohydrate. This water retention in some instances is sufficient to lead to a visible edema, although the greater part of the water retained is probably stored in the body in colloid combination with glycogen.

PROTEIN DIGESTION

Schackwitz²⁴ finds a sufficient amount of acid present in the gastric juice of infants to render peptic digestion of casein possible. He determined no essential difference between the gastric juice of artificially fed and of breast-fed infants. Finzio²⁵ claims that the gastric juice of normal infants after four hours' fast is capable of digesting casein. The juice removed at intervals of thirty, sixty, ninety, and 120 minutes after feedings of either woman's milk or cow's milk is also able to digest considerable quantities of milk protein. He concludes that the gastric juice of an infant is quite as effective in digesting the proteins of milk as is the adult gastric juice in digesting egg white. He draws attention to the work of previous observers who have found what they believe to be an insufficient amount of hydrochloric acid present in the gastric juice to activate pepsin, but maintains from the results of his experiments that free hydrochloric acid is not an essential for the peptic digestion of the proteins of milk.

PROTEIN ABSORPTION

A number of observers have endeavored to determine if protein can be absorbed through the intestinal wall without previous hydrolysis. Hayashi²⁶ administered from 15 to 20 gm. of raw egg albumin to normal infants, but failed to detect any albumin in the urine. Many infants suffering from eczema and from digestive disturbances, however, excreted protein in the urine after the ingestion of relatively small quantities of egg albumin.

Lawalschek,²⁷ by means of the precipitin reaction applied to the urine, determined that the intestinal tract of all infants under 10 days of age allows the passage of undigested foreign proteins. The permeability becomes less with age, but is increased during the course of nutritional disturbances. Modigliani and Benini²⁸ have confirmed the

24. Schackwitz: *Monatsch. f. Kinderh.*, 1914, xiii, 73.

25. Finzio: *La Pediatria*, 1915, xxiii, 95, 168.

26. Hayashi: *Monatschr. f. Kinderh.*, 1914, xii, 749.

27. Lawalschek, R.: *Prag. med. Wchnschr.*, 1914, x1, 185.

28. Modigliani and Benini, *Policlinico*, Rome, December, 1915.

findings of Lawalschek as to the absorption of undigested protein in nutritional disorders. Schloss and Worthen²⁹ studied the absorption of unchanged protein by means of anaphylactic and precipitin reactions applied to the blood and urine. They found that when foreign protein is absorbed unchanged it appears in the blood sooner than in the urine, but that its presence may be detected in the urine for a longer time than in the blood. They found no evidence of absorption of whey protein from the intestinal tracts of the normal infants studied. Atrophic infants and those suffering from gastrointestinal disturbances, however, excreted whey protein in the urine. Egg protein they found at times to be absorbed unchanged by the normal infant's intestinal mucosa, when fed in large quantities, but not when moderate quantities were given. They state that in gastrointestinal disorders egg protein is frequently absorbed unchanged. The more severe the disorder, the greater the permeability of the gastro-intestinal tract. With improvement in the condition the permeability disappears. Of infants with eczema, 50 per cent. showed absorption of unchanged protein. Schloss and Worthen further attempted to demonstrate the presence of specific proteolytic enzymes in the blood serum. According to Abderhalden's hypothesis, the parenteral absorption of foreign proteins results in the formation of protective enzymes capable of hydrolyzing protein. These enzymes are presumably specific for the protein in question. Schloss and Worthen, following the technic advised by Abderhalden for the demonstration of specific proteolytic enzymes in the blood in pregnancy, were able to demonstrate enzymes capable of hydrolyzing milk and egg proteins in the blood of many normal infants. The occurrence of such enzymes, however, was more frequent in the blood of infants suffering from nutritional disorders. It is noteworthy that the blood from a number of infants who had never been fed egg proteins contained enzymes capable of hydrolyzing egg protein; this finding would seem to be a refutation of Abderhalden's hypothesis.

INTERMEDIARY METABOLISM OF PROTEIN

Hoobler³⁰ has studied the effect of low and high protein diets in infants and finds that protein when fed in excess causes an increase in the energy metabolism and that the increase is in proportion to the amount of protein oxidized and not to the amount of protein fed or retained in the body. Excessive feeding of protein does not reduce the amount of fat and carbohydrate metabolized, but the fat and carbohydrate need remains fairly constant and unless this minimal need is supplied in the food, the organism draws on its stored-up fat and glycogen, even when large amounts of protein are fed. When protein is fed in excess to infants a condition of stupor may supervene,

29. Schloss and Worthen: *AM. JOUR. DIS. CHILD.*, 1916, xi, 342.

30. Hoobler: *AM. JOUR. DIS. CHILD.*, 1915, x, 153.

which assumes serious proportions if such feeding is continued. The stupor gradually disappears as protein is reduced in the diet. The condition is considered by Hoobler to be a protein food injury and to constitute a clinical entity as definite in its symptomatology as that which arises from too prolonged use of diets high in carbohydrates. Hoobler claims that the protein need of a growing infant is completely supplied when 7 per cent. of its caloric need is furnished in the form of protein.

Cathcart and Green³¹ found that in the metabolism of protein, the sulphur-containing groups are more quickly split off and eliminated than the rest of the molecule. Cohnheim³² finds that completely hydrolyzed proteins, such as erepton, behave in the intestinal tract and in the intermediary metabolism exactly as unchanged protein.

Eisner³³ finds that protein metabolism, as determined by the neutral sulphur excretion, is disturbed when fats are eliminated from the diet, but is not at all influenced by changes in the carbohydrate intake.

Hellesen⁵ finds that nitrogen retention in infants is less when the fat of the diet is increased and the carbohydrate decreased.

Cutter and Morse³⁴ found in a 2 year old infant that creatin elimination entirely ceased during a period of loss of weight dependent on vomiting, but again reappeared in the urine when the infant began to gain in weight. The creatinin elimination remained normal throughout. This finding is in contrast to the findings that have previously been reported on adults, in whom fasting and loss of weight is accompanied by increased creatin elimination and suggests a distinct difference in the intermediary protein metabolism of the infant and of the adult.

NITROGENOUS CONSTITUENTS OF THE BLOOD

Tileston and Comfort³⁵ found the nonprotein nitrogen and urea of the blood of children to be the same as that of adults. Schlutz and Pettibone³⁶ studied the nitrogenous compounds in the blood of newly born infants. They found the total nonprotein nitrogen varied from 23 to 44 mg., the urea nitrogen from 8 to 24 mg., ammonia nitrogen from 0.2 to 0.6 mg. and the amino-acid nitrogen as determined by the Van Slyke method, from 0.3 to 0.6 mg. per 100 gm. of blood. They draw attention to the fact that amino-acid nitrogen is frequently found in the blood in appreciable amounts even before the infant had received any food. They consider this finding as an indication of the passage of amino-acids from the maternal into the fetal blood. Nobécourt³⁷

31. Cathcart and Green: *Biochem. Jour.*, 1913, vii, 1.

32. Cohnheim: *Ztsch. f. physiol. Chem.*, 1913, lxxxiv, 419.

33. Eisner: *Dissertation Erlangen*, 1913.

34. Cutter and Morse: *AM. JOUR. DIS. CHILD.*, 1916, xi, 331.

35. Tileston and Comfort: *AM. JOUR. DIS. CHILD.*, 1915, x, 278.

36. Schlutz and Pettibone: *AM. JOUR. DIS. CHILD.*, 1915, x, 206.

37. Nobécourt: *Arch. de méd. d. enfants*, 1914, xvi, 801.

determined the urea in the cerebrospinal fluid and found normally that the amount was never greater than 0.5 per cent. In nutritional disorders he observed increases in the urea content of the cerebrospinal fluid and considered this as evidence of increased protein destruction rather than of renal retention.

NITROGENOUS CONSTITUENTS OF THE STOOLS

Gamble³⁸ found the average amount of ammonia nitrogen in the stools of approximately normal infants to be 4.2 mg. per gram of dried stool, or 9 per cent. of the total nitrogen. The total amount of ammonia nitrogen increases with the protein intake. According to him, constipated stools contain the least ammonia, both relatively and absolutely. In malnutrition high amounts of ammonia were found. Urea was constantly found, although in very small amounts, the average urea nitrogen being 2 mg. per gram of dried stools. There seemed to be no constant relationship between the amounts of urea nitrogen and of ammonia nitrogen. Gamble suggests that the urea of the stools may not be entirely the result of excretion through the intestinal wall, but may be produced in the intestine by bacterial activity. His finding that the urea content of stools increases on standing would seem to lend support to this hypothesis.

Van Slyke, Courtney and Fales³⁹ state that the ammonia nitrogen of the stools makes up from 4 to 37 per cent. of the total nitrogen. They were unable to find any relationship between the amount of ammonia and the state of nutrition of the infant, or between acidity and the ammonia content of the stools. Urea was not found in 75 per cent. of the stools examined; when present the urea nitrogen made up from 1 to 5.6 per cent. of the total nitrogen. These authors do not believe that urea is secreted from the intestinal wall, as the urea was frequently absent in very loose stools. The amino-acid nitrogen made up from 1.8 to 17.6 per cent. of the total nitrogen. The stools of normal infants contained less amino-acid nitrogen than did those of infants with diarrhea.

Weill and Dufour¹⁷ found that the feeding of relatively large amounts of protein to infants passing acid stools caused the stools to become neutral or alkaline in reaction.

FAT METABOLISM

Giffhorn⁴⁰ finds that the formation of soap stools may be prevented by the addition of whey to the diet.

Holt, Courtney and Fales⁴¹ find that the fat content of the stools varies in most cases directly with the water content. In general, a

38. Gamble: *AM. JOUR. DIS. CHILD.*, 1915, ix, 519.

39. Van Slyke, Courtney and Fales: *AM. JOUR. DIS. CHILD.*, 1915, ix, 533.

40. Giffhorn: *Jahrb. f. Kinderh.*, 1913, lxxviii, 531.

41. Holt, Courtney and Fales: *AM. JOUR. DIS. CHILD.*, 1915, ix, 213.

child losing twice as much water by the bowel is usually losing twice as much total fat. They observed, however, at times, a very high fat loss in dry, formed, soapy stools. The percentage of fat expressed in terms of fatty acid averaged 37.7 per cent. of the dried matter in very loose stools. The form of fat differed very much in the different types of the stools. In normal pasty stools the soap fats were present in larger amounts than neutral fat. In loose stools the ratio was reversed; in some very loose stools soaps were entirely absent, the neutral fat being at the same time greatly increased.

Hellesen⁵ finds that when fat is substituted for an isodynamic amount of carbohydrate in the diet, marked alterations occur in the total heat production and in the metabolism of protein, mineral matter and water. These alterations are discussed elsewhere in this review.

MINERAL METABOLISM

Holt, Courtney and Fales⁴¹ find that under normal conditions 40 per cent. of the total ash taken in cow's milk is lost in the stools. This is chiefly calcium phosphate. In loose stools as much as 84 per cent. of the intake may be lost, the great increase being made up of salts other than calcium phosphate. Chlorin, potassium, and sodium were found normally present in stools in relatively small amounts, but in large amounts in the urine. In loose stools there was an enormous increase in the quantity of these elements and a corresponding reduction in the amount eliminated by the urine. The increased excretion by the bowel, however, was so great that there was observed an actual negative balance of sodium and potassium.

Courtney and Fales⁴² found that after injection of magnesium sulphate, subcutaneously, a very small amount of the magnesium was eliminated by the way of the bowels. The greater part appeared in the urine within twenty-four hours. None appeared on subsequent days. The sulphate portion of the molecule was immediately and completely excreted in the urine. Courtney and Fales do not believe that there is any danger of a cumulative effect of magnesium sulphate following repeated injections.

Bosworth, Bowditch and Ragle⁴³ studied the effects of varying the mineral intake by increasing or decreasing the whey of the food. They found that when the whey was decreased a less acid urine was secreted. The inorganic phosphates of the urine were decreased and the chlorid completely disappeared. There was a rise in the ammonia coefficient in the urine, due, as they believed, to the lack of bases in the food, as they found no increase in the production of acetone bodies. The infants studied lost weight during the time that they were fed on the diets poor in whey. The authors do not believe that the loss in weight

42. Courtney and Fales: *AM. JOUR. DIS. CHILD.*, 1915, ix, 318.

43. Bosworth, Bowditch and Ragle: *AM. JOUR. DIS. CHILD.*, 1915, ix, 120.

can be explained on any other ground than on that of mineral deficiency.

Kaminer and Mayerhofer⁴⁴ found that the inorganic phosphate excretion in the urine of infants increases during digestive disturbances and also following an increase in the concentration of the food, after the addition of sugar or cereal and on changing from breast milk to artificial feeding. Knox and Tracy⁴⁵ confirmed Kaminer and Myerhofer's findings as to the greater excretion of the phosphates in the urine of the artificially fed infants. They do not believe, however, that any conclusions can be drawn as to the nutritional disturbances from the urinary phosphate excretion.

Peiser⁴⁶ found an increase in the phosphorus and sulphur elimination by way of the bowel and a decreased elimination by the urine, when protein milk was substituted for breast milk in the feeding of a normal infant, and attributes the increased sulphur and phosphorus of the stools to a failure of absorption. Hellesen⁵ finds that on diminishing the carbohydrate in the food of an infant and substituting an isodynamic quantity of fat, absorption of mineral matter from the intestinal tract is somewhat less, the absorption of calcium being affected more than that of the other inorganic constituents of the food. Ash retention is much less on the diet rich in fat, there being a marked increase in excretion of mineral matter by the urine. The loss of sodium in the urine is four times as great as with the low fat diet and is actually greater than the amount ingested. Smaller amounts of potassium, of calcium and of chlorine are retained. The retention of magnesium and of phosphoric acid is about the same with each diet.

WATER METABOLISM

A number of investigators have studied the water balance of infants. Benestad⁴⁷ attributes the loss of weight of newly born infants to disturbances in the water metabolism. Lederer⁴⁸ determined the water content of the blood of infants by a micromethod. He found that the blood in a normal breast fed infant at birth has a low water content; the water increases rapidly during two or three months, reaching a maximum at the middle of the third month. After this time a gradual but slow drying out occurs. He draws attention to the fact that the increase in the water content of the blood runs parallel with the rapid increase in water intake during the first three months.

44. Kaminer and Mayerhofer: *Ztschr. f. Kinderh.*, 1913, viii, 24.

45. Knox and Tracy: *AM. JOUR. DIS. CHILD.*, 1914, vii, 409.

46. Peiser: *Jahrb. f. Kinderh.*, 1915, xxi, 437.

47. Benestad, G.: *Jahrb. f. Kinderh.*, 1914, lxxx, 21.

48. Lederer: *Ztschr. f. ang. Anat. u. Konst.*, 1914, i, 298.

Infants fed on whole milk dilutions show a greater water content of the blood and a decreased physiologic drying out. In eczema he frequently observed rapidly occurring fluctuations in the water content of the blood. Hellesen⁵ finds a negative water balance following the substitution of fat for a portion of the carbohydrate of the diet of an infant.

Widmer⁴⁹ finds that when the total fluid intake, including the water of solid food, is reduced to 65 gm. per kilogram, no unfavorable symptoms appear and infants from 1 to 2 years old continue to thrive. He considers 65 gm. per kilogram to be the minimum water requirement. When the water intake is increased to 110 gm. per kilogram, disturbances in weight and nutrition frequently occur. He considers the optimal water intake to be 85 gm. per kilogram and states that too much water leads to nutritional disturbances, especially rickets, tetany and eczema.

Niemann³ finds the water vapor output of the body to be roughly proportional to body weight and not to surface area.

ACETONE BODIES

Veeder and Johnson⁵⁰ find small amounts of ketones (presumably acetone) and beta-oxybutyric acid present in the urine of normal children, even when their caloric requirements are fully covered by the diet. The amount varies from 20 to 100 mg., expressed in terms of acetone in twenty-four hours. Age, sex and body weight of the child apparently have no effect on the total amount excreted. The amount of beta-oxybutyric acid excreted is, as a rule, greater than the amount of acetone. They consider the large amount of acetone bodies in the urine of children on restricted diet to be due to an increase of substances normally present, rather than to the appearance of abnormal substances. Veeder and Johnson's results show the fallacy of the common belief, based on the incorrect interpretation of qualitative tests, that acetone appears in the urine in larger amounts than oxybutyric acid and that oxybutyric acid excretion is an evidence of a severe metabolic derangement.

Marriott⁵¹ finds in the blood of normal children from 0.5 to 1.1 mg. of acetone and diacetic acid and 1.4 to 4.4 mg. of oxybutyric acid, expressed in terms of acetone per 100 gm. of blood, and emphasizes the frequent disproportion between the amounts of acetone substances in the blood and the amounts in the urine.

49. Widmer: *Jahrb. f. Kinderh.*, 1916, lxxxiii, 177.

50. Veeder and Johnson: *AM. JOUR. DIS. CHILD.*, 1916, xi, 245.

51. Marriott: *Jour. Biol. Chem.*, 1914, xviii, 507.

OXALIC ACID

Sedgwick⁵² finds that newly born infants excrete as much as 9 mg. of oxalic acid per day. The amount is relatively and at times absolutely greater than the excretion of oxalic acid by adults.

PSYCHIC FACTORS AND TEMPERATURE

Birk⁵³ emphasizes the influence of psychic factors on the metabolism and cites cases of children on the same diet thriving well or poorly depending on the nurse in charge. He explains "hospitalism" on the psychic basis. McClure and Sauer⁵⁴ find that an infant with ordinary light clothing in a room at a temperature of 31 C. is practically incapable of losing heat by either conduction or radiation. Experiments with puppies clothed in flannel and subjected to similar temperatures indicate that this failure of heat loss may lead to severe symptoms or even to a fatal termination.

52. Sedgwick, J. P.: *AM. JOUR. DIS. CHILD.*, 1915, x, 414.

53. Birk, W.: *Monatschr. f. Kinderh.*, 1913, xii, 1.

54. McClure and Sauer: *AM. JOUR. DIS. CHILD.*, 1915, ix, 490; *Ibid.*, x, 425.

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THE EFFECT OF SUBCUTANEOUS INJECTIONS OF MAGNESIUM SULPHATE IN CHOREA *

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The existence of the condition termed chorea has been well known ever since the Middle Ages. For centuries the medical profession has endeavored to treat it satisfactorily, as well as to explain its etiology. The results so far have been disappointing. Sedatives, such as bromids and chloral, the salicylates, rest, hydrotherapy, and hygienic measures, all have a beneficial influence on certain symptoms in chorea. Arsenic, however, in this condition is a greatly overestimated drug; I have yet to see it relieve, even in the slightest degree, the choreic manifestations or shorten the course of the disease. We are still sadly in want of a specific remedy to cope satisfactorily with this annoying, chronic, and occasionally serious malady.

In the absence of positive knowledge as to the causation of chorea, it is justifiable to attempt symptomatic treatment alone, with the view of lessening the severity and frequency of the choreic manifestations and rendering the patient more comfortable. Stimulated by the work of Meltzer in the treatment of tetanus by injections of magnesium sulphate, I applied a similar method in a series of chorea cases, in the hope that a favorable influence would be exerted on the psychomotor system.

Meltzer investigated the effect of various salts on animals and human beings and found that of magnesium sulphate unmistakably inhibitory in character. Various modes of administration were investigated—intravenous, intraspinal, intramuscular, and subcutaneous. In intravenous and intramuscular injections the effect was rapid, but of short duration; in intraspinal injections, rapid and of longer duration; in subcutaneous injections, slow and of still longer duration, with the possibility of a cumulative action. Meltzer claims that in tetanus there is no other remedy capable of relieving the very severe convulsive symptoms so satisfactorily as the injection of magnesium sulphate. To explain the inhibitory phenomena exerted by magnesium sulphate in tetanus, he offers the hypothesis that the magnesium solution contained in the lymphatic circulation enters into the spaces, or, as termed by Sherrington, "synaptic membrane," between the various neurons or between neurons and muscle, and thus interrupts the passage of afferent

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impulses. He concludes that magnesium sulphate by subcutaneous injections should be given in every case of tetanus.

Chorea, though entirely dissimilar in etiology, in pathology, and in symptomatology to tetanus, is characterized by irregular, incoordinate muscular movements, which in turn depend on some pathologic condition of the psychomotor system, probably central in origin. Reasoning from analogy, therefore, I regarded it possible that magnesium sulphate might have a similar beneficial effect in chorea, and that a trial in a series of cases would be warranted. Feliziani and Natali have used intraspinal injections of magnesium sulphate in chorea with doubtful results. The latter had seven cases of chorea minor and one case of chronic chorea in which this method of therapy was employed. He claims that three patients were entirely, and four nearly, cured, but that the chronic case was not modified. Even if this method of therapy were but empirical and had not a possible theoretical foundation, no apology would be necessary for employing it in an endeavor to find a remedy for this obscure condition which has for so long baffled medical science. That the results were disappointing in chorea does not in any way speak against the use of magnesium sulphate in tetanus, in which disease excellent results have been obtained. If chorea is a direct sequel of rheumatism, influenza, scarlatina, or other infections, it is possible that no remedy will be of any avail until the respective toxins have been thoroughly eliminated from the system in each case, and the damage done to the nervous system healed by the natural and gradual processes of repair.

METHOD AND TECHNIC OF INJECTION

Five successive patients with chorea from the children's service of Dr. Koplik at Mt. Sinai Hospital were treated by repeated subcutaneous injections of magnesium sulphate. In every case a 25 per cent. sterile solution was used. The dose ranged from 0.01 gm. magnesium sulphate per kilogram of body weight (that is, 0.04 c.c. of the 25 per cent. solution) at the beginning of treatment, with a daily increase to 0.2 gm. magnesium sulphate per kilogram of body weight (that is 0.8 c.c. of the 25 per cent. solution) at the termination of treatment. The actual amounts of solution used daily were from 3 to 30 c.c. The injections were given three times daily for from ten to fifteen days, with the ordinary record syringe, into the back, loins and buttocks of the patients.

EFFECT OF TREATMENT

The table gives in brief the important data regarding the cases under observation. In only one of the five patients treated by this method was there a marked improvement after the series of injections, and in this case the choreic movements gradually diminished, the child

became less irritable and general improvement was noted. It is very questionable whether or not the improvement was directly due to the treatment; it is possible that it was purely coincidental and the result of natural processes. In the four other cases there was no improvement, the magnesium sulphate having had apparently no effect whatever on the psychomotor system. In all events the results of the treatment in the small series of cases was not sufficiently promising in my opinion to justify a continuation of the treatment.

DATA OF FIVE PATIENTS TREATED FOR CHOREA BY MAGNESIUM SULPHATE

Name	Age, Yrs.	Duration before Admission, Wk.	Severity	Dose MgSO ₄ per Kg. Body Weight, Gm.	Period, Days	Number of Injections	Results
A. L.	8	3	Moderate	0.01 to 0.2	11	44	No improvement
I. D.	5	2	Severe	0.01 to 0.055	11	40	Slight improvement
B. K.	9	5	Moderate	0.02 to 0.2	13	45	No improvement
E. O.	10	6	Severe	0.01 to 0.05	11	37	Considerable improvement
E. W.	10	1	Mild	0.01 to 0.2	11	44	Slight improvement

* All the patients were girls.

There are, however, certain decided objections to the use of this method. The quantity of solution used, especially at the termination of treatment, is so large that there is a possibility of an inflammatory reaction, even abscess formation. We did not have any accident of this nature, however, in our cases. Occasionally the patients, especially if very young, are likely to be unduly excited by the treatment itself. Another disadvantage is the possibility of having the needle broken off in the tissues during the administration of the solution, on account of the marked restlessness of the patient. Albuminuria has been reported by several observers after the injection of magnesium sulphate. In our cases albumin was noticed in several instances, but this condition disappeared after a short interval. This treatment, even if effective, would be best employed in hospitals, inasmuch as three or four injections daily by skilled hands would be required.

CONCLUSIONS

Subcutaneous injections of magnesium sulphate, though employed in only five cases, did not produce sufficient improvement to justify further trial.

I take this opportunity to thank Dr. L. G. Shapiro, formerly house physician of Mt. Sinai Hospital, for his painstaking assistance in this work.

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A STUDY OF NORMAL AND PATHOLOGIC CEREBRO-SPINAL FLUIDS IN CHILDREN *

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INTRODUCTION

This investigation has been undertaken to determine the relative value of various methods in use in the examination of the cerebrospinal fluid in sundry affections of the central nervous system of children.

The differentiation of true meningitis from serous meningitis by means of the cell content of the cerebrospinal fluid has been established by the introduction of lumbar puncture. Furthermore, the causative organism in various types of meningitis has been demonstrated by bacteriologic methods. It was at first believed that a diagnosis of tuberculous meningitis might be established by a characteristic increase in the number and type of cells found in the fluid, but it was later shown that the number of cells in this condition is subject to wide variation, and that there are a number of conditions which give the same cytologic findings, namely, encephalitis, acute anterior poliomyelitis, meningismus, syphilis of the central nervous system and tuberculous meningitis. In the last-named condition, then, we must have the added test of demonstrating tubercle bacilli in the cerebrospinal fluid to establish a diagnosis. This is possible in a large percentage of cases, but not invariably so.

Owing to the fact that clinical manifestations and microscopic findings in the cerebrospinal fluid in certain affections of the central nervous system were not adequate for ascertaining the nature of the process, the necessity for chemical and serologic methods of examination was obvious. This led to the development of methods for the qualitative determination of globulin in the cerebrospinal fluid by Nonne,¹ Ross-Jones,² Pandey,³ and Noguchi.⁴ These methods have all been advanced as an aid in the diagnosis of syphilitic affections of the central nervous system. Each has its distinct value as a means of

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1. Nonne: Syphilis and the Nervous System, p. 341.

2. Ross-Jones: Brit. Med. Jour., 1909, i, 1111.

3. Pandey: Neurol. Centralbl., 1910, xxix, 915.

4. Noguchi: Serum Diagnosis of Syphilis, Ed. 2, p. 155.

determining the presence of globulin, which is found in the cerebrospinal fluid in a number of conditions, and is generally conceded to be the result of and indicative of some inflammatory process affecting the meninges. The various tests showing the presence of globulin do not give any selective reaction, but vary somewhat in delicacy, and their intensity is dependent on the degree of inflammatory involvement. The exudation of globulin in the cerebrospinal fluid is usually accompanied by an exudation of cells, but globulin is not infrequently present without an increase of the latter. The application of the Wassermann reaction to the cerebrospinal fluid in syphilis of the central nervous system has proved invaluable.

In 1912 Lange⁵ introduced the colloidal gold reaction, the specific significance of which is now well recognized by a large number of observers, although the exact nature of the reaction is still somewhat uncertain. Among the more recent publications on this subject, one by Miller⁶ and his co-workers gives an exhaustive treatise on the development of the colloidal gold reaction from the early experiments of Zsigmondy to the practical application of this work as a diagnostic method in examination of the cerebrospinal fluid by Lange. Since its introduction observations on the gold chlorid reaction have accumulated from many sources. A summary of these leads us to conclude that there is a specific reaction in a pathologic cerebrospinal fluid, and that the test is a valuable adjunct to the present laboratory and clinical methods. The reaction is dependent on the presence of protein substances, and like the various globulin tests, is indicative of an inflammatory process in the meninges. However, it is not to be questioned that the reaction is to a certain extent selective, because of the uniform evidence of a specific reaction given by syphilitic cerebrospinal fluids, more particularly those from patients with general paresis.⁷

The test is generally conceded to be more delicate than the Wassermann reaction on the cerebrospinal fluid, when the reaction (precipitation of the colloidal gold) occurs in the so-called "syphilitic zone."⁸ There has been no selective reaction observed in nonsyphilitic conditions and it is concluded that the test has no specific diagnostic import in many obscure affections. The occurrence of a positive reaction, however, does indicate a pathologic cerebrospinal fluid.

5. Lange: *Zentralbl. f. Chemotherapie*, 1912, i, 44; *Berl. klin. Wchnschr.*, 1912, xlix, p. 667.

6. Miller, Brush, Hammers and Felton: *Bull. Johns Hopkins Hosp.*, 1915, xxvi, 391.

7. For the bibliography and summary of this subject, the reader is referred to the work of Miller, Brush, Hammers and Felton, Footnote 6.

8. Solomon, Koefod and Welles (*Boston Med. and Surg. Jour.*, 1915, clxxiii, 956) consider the term "syphilitic zone" a misnomer, because of a number of different conditions giving reactions in the lower dilutions.

The occurrence of a substance in the cerebrospinal fluid which reduces Fehling's solution has been considered of diagnostic import because of its absence in various types of meningitis. Schloss⁹ has published evidence to show that this reducing substance is dextrose and that the quantity varies within a relatively wide range in normal fluids and may be normal in quantity or decreased in tuberculous meningitis. Its absence in fluids from patients with purulent meningitis is well known. Most observers agree that this reducing substance is present in all clear fluids, hence its mere qualitative determination can have little significance in diagnosis.

The reduction of potassium permanganate by the organic substances of the cerebrospinal fluid has been utilized as a diagnostic method by Mayerhofer¹⁰ and Neubauer¹¹ and has been mentioned as an aid to diagnosis in a case report by Lackner and Levinson.¹²

The amount of tenth-normal potassium permanganate reduced by 1 c.c. of cerebrospinal fluid is considered as the reduction index of the fluid. Hoffman and Schwartz¹³ found that normal fluids, or fluids from patients presenting meningeal symptoms without actual inflammation of the brain or meninges, give low permanganate indexes (2 c.c. and less), and that borderline indexes (from 2 to 2.5 c.c.) occur in the early stages of an inflammatory process. They conclude that the reduction index has a distinct value in the examination of the cerebrospinal fluid.

TESTS SELECTED—TECHNIC

The routine examination of the cerebrospinal fluids in this work included the cell count, the determination of globulin by the methods of Nonne and Noguchi, the reduction of Fehling's solution, the reduction index of potassium permanganate, and the colloidal gold test. The Wassermann test was made only on those fluids in which there was some definite indication.¹⁴ All fluids containing blood were rejected.

1. Cell Count: The cells were counted in the Thoma-Zeiss chamber. The pipet was rinsed with glacial acetic acid before filling with the fluid, to facilitate the differentiation of the nuclei. In a number of fluids a mixture of equal parts of glacial acetic acid and Wright's stain was drawn up to the 0.1 mark in a white cell pipet, which was then filled with fluid. This method has no advantage over the simple acetic acid method.

9. Schloss: *AM. JOUR. DIS. CHILD.*, 1916, xi, 1.

10. Mayerhofer: *Wien. klin. Wchnschr.*, 1910, xxiii, 651.

11. Neubauer: *Ztschr. f. Kinderh.*, 1911, iii, 2.

12. Lackner and Levinson: *Arch. Pediat.*, July, 1915, xxxii, 508.

13. Hoffman and Schwartz: *Arch. Int. Med.*, 1916, xvii, 293.

14. For this work I am indebted to Drs. Olmsted and Flexner of the Department of Internal Medicine.

2. Globulin: (a) The globulin test of Noguchi was made according to the original description, 0.2 c.c. of fluid was boiled with 0.5 c.c. of 10 per cent. butyric acid and reheated after the addition of 0.1 c.c. of 4 per cent. potassium hydroxid. (b) The test of Nonne was made by adding 1 c.c. of a saturated solution of ammonium sulphate to 1 c.c. of cerebrospinal fluid. The ammonium sulphate is added slowly, so that a definite line of contact is formed. This is allowed to stand for one minute and observations are made for a precipitation at the line of contact. It is then completely mixed and observations are again made.

3. Lange Reaction: The difficulties and sources of error in the technic of the preparation of the colloidal gold reagent have no place in the present discussion. Suffice it to say that these difficulties are not great enough to warrant the abandonment of the test as a routine of cerebrospinal fluid examination. The test itself may be made easily and rapidly. Ten dilutions of the cerebrospinal fluid are made with 0.4 per cent. sodium chlorid ranging from 1 to 10, 1 to 20, 1 to 40 and so on to 1 to 5,120, and 1 c.c. of each dilution is used. An eleventh tube containing 1 c.c. of 0.4 per cent. sodium chlorid serves as a control. To each tube 5 c.c. of the colloidal gold reagent is added. After from ten minutes to one hour the characteristic color changes appear; after this time there is intensification of the colors, and the readings are best made twelve to twenty-four hours after the beginning of the reaction. The reagent has a bright orange-red color and the changes which occur are to a red-blue, purple (violet), blue, pale blue, and colorless; the intensity of the color change is expressed, in recording, by the numerals 1, 2, 3, 4, and 5 respectively. This method of recording has been explained in other publications and is quite uniform for all observers.

5. Permanganate Index: To 1 c.c. of the cerebrospinal fluid in a suitable flask, 50 c.c. of double distilled water and 10 c.c. of dilute sulphuric acid (concentrated sulphuric acid 1 part, water 3 parts) are added and the mixture is heated to the boiling point. Ten c.c. of tenth-normal potassium permanganate are added, and the boiling is continued for exactly ten minutes. At the end of this time 10 c.c. of tenth-normal oxalic acid is added; on the addition of this, the solution becomes clear and the excess of oxalic acid is titrated with tenth-normal potassium permanganate to a faint pink end-point. This result gives the amount of potassium permanganate which has been reduced by the fluid examined and is known as the reduction index. As a control, 50 c.c. of water with 10 c.c. of the dilute sulphuric acid must be treated in the same way to determine their reducing activity at the time used. This has varied between 0.6 and 1.2 c.c. of potassium permanganate

at different times and is subtracted from the index given by the cerebrospinal fluid. The difference represents the true reduction index of the fluid examined.

COMMENT

One hundred and nineteen fluids were examined from 100 patients, and in each case laboratory and clinical findings were carefully correlated. Without reference to the clinical diagnosis, evidence of pathologic change in the fluids examined may be summed up as follows:

	No. Examined	Positive	Per Cent.
Cell count	118	45 (pleocytosis)	38
Noguchi	119	53	44
Nonne	119	32	27
Lange	119	71	60
Wassermann reaction	54	15	28
Fehling's	118	19 (negative)	16
Permanganate index	110	80 (more than 2)	72

The occurrence of globulin in the cerebrospinal fluid together with an increase in the cell content is undoubted evidence of an inflammatory process affecting the meninges, and pleocytosis, the Noguchi reaction, and the Nonne reaction show a close relation, though it is evident that the Noguchi globulin test is far more delicate than that of Nonne. In those fluids showing a normal cell count and a positive Noguchi globulin reaction the indication was usually faint. In only one instance was there an increased cell content with a negative Noguchi, and this fluid was from a child with brain abscess, two days later the fluid showing changes characteristic of a purulent meningitis. I have observed no selective action in either the Noguchi or Nonne tests in showing the presence of globulin in pathologic cerebrospinal fluids. The occurrence and intensity of the reaction has seemed rather to depend on the amount of globulin present. In advanced conditions the cell content gives more accurate information concerning the nature of the process.

Granting that the colloidal gold reaction is a test for the presence of protein substances and therefore evidence of pathologic change in the cerebrospinal fluid, as is generally conceded, it is unquestionably more delicate than the other tests here used for comparison. This has been the experience of all observers. Every fluid showing the presence of globulin gave a positive Lange reaction. Of eleven questionable colloidal gold reactions, six were bizarre reductions, accounted for only by errors in technic and not likely to cause confusion, and have been considered negative. Five were from children with hereditary syphilis, and the fluids caused only a slight reduction in the syphilitic zone.

There has been noted a certain parallelism between the reduction of the colloidal gold in the various dilution zones and the amount of globulin in the fluid, as estimated by the intensity of the Noguchi and Nonne reactions. That is, those showing only a trace of globulin or none at all reduce the lower dilutions. Those with a higher content reduce the higher dilutions. Such a crude quantitative estimation, of course, is not at all satisfactory, and the amount of coagulable and noncoagulable nitrogenous bodies should be determined before any conclusions are drawn.

That there may be some specific selective action of a substance in the pathologic fluid, without definite relation to quantity, is very probable, because of the uniform evidence of the existence of a typical "paretic curve," occurring with fluids from patients with general paresis.

The reduction of Fehling's solution by the cerebrospinal fluid is of interest chiefly because of its negative value in reference to diagnosis. The amount of reduction varies in normal fluids and reduction has occurred in tests on all pathologic fluids except those from patients with purulent meningitis and advanced tuberculous meningitis. If the presence of dextrose in the cerebrospinal fluid is to be of any value in diagnosis, its estimation must be quantitative.

The high incidence of a permanganate index of more than 2 leads to the evident conclusion that this value can not be taken as a criterion for normal fluids. Of 110 fluids on which this test was made, forty-three were normal, as indicated by a normal cell count and a negative colloidal gold test. The reduction index of these normal fluids varied between 1.4 and 2.7 with an average of 2. In thirty-six fluids taken from patients with syphilis and acute anterior poliomyelitis, showing slight pathologic change, the variation was from 1.4 to 2.9, with an average of 2.4. In more marked meningitic processes the average is found to be definitely higher. In any condition, though, the individual variations are so great that no significance can be placed on a slightly increased permanganate index. Moreover, there is noted no definitely increased index in the early stages of the more severe meningeal inflammation when the test might be of clinical value, the high index occurring only in advanced conditions, in which the nature and cause of the changes are evident.

The reduction of potassium permanganate depends on two factors, namely, the dextrose and nitrogenous bodies. Even in normal fluids the amount of sugar is variable, and this may be true of the nitrogenous bodies. This may explain the wide limits of variation in the reduction index. With a slight increase of protein substance the dextrose may be normal or slightly reduced, hence the lack of uniformity in the indexes of fluids showing little pathologic change. It is only those

TABLE 1.—SYPHILIS

No.	Name	Cell Count	Globulin		Fehling's	Permanganate Index	Lange	Wassermann Reaction	Remarks
			Noguchi	Nonne					
3	E. B.	6	0	0	++	1.4	$\pm 2331 \pm 0000$	++++	Six months later
50	E. B.	30	\pm	0	+	2.5	22332 ± 0000	++++	
10	G. McD.	5	\pm	0	++	2.1	$\pm 24443 \pm 000$	++++	
18	E. B.	25	+	0	++	2.9	12341 ± 1100	++	Seven months later
28	G. D.	1	0	0	+	2.3	$\pm 2111 \pm 000$	++++	
62	G. D.	4	0	0	++	2.7	33332 ± 0000	+	
29	C. S.	6	0	0	+	2.6	333210000	++++	
36	E. G.	1	0	0	+	2.5	$0 \pm 22 \pm 00000$	0	
52	I. W.	45	++	+	+	2.4	5455332 ± 00	++++	One week later
57	I. W.	40	+	+	+	2.3	5554431000	—	
60	P. B.	5	0	0	++	2.9	444432 ± 000	0	
61	A. C.	1—	0	0	+	2.5	4554431 ± 00	0	
64	H. H.	19	+	0	+	2.7	55554 ± 0000	++++	
66	M. G.	3	0	0	+	2.1	$\pm 122 \pm 00000$	0	
76	W. N.	5	+	0	++	2.3	233332 ± 000	0	
80	R. S.	8	+	0	++	2.3	3883000000	—	

fluids showing a large increase of protein which give a definitely increased permanganate index.

The discussion of the Wassermann reaction on the cerebrospinal fluid has been reserved for consideration in comparison with the other findings in the fluids from cases of hereditary syphilis. In all, thirty-six fluids were examined from thirty-one patients with hereditary syphilis, in all of which the Wassermann reaction on the blood was positive. The colloidal gold showed varying degrees of reduction with the majority of these fluids, and this occurred in the syphilitic zone in every instance but three (Nos. 95, 97, 111).¹⁵ In five of the reactions (Nos. 28, 36, 66, 110, 114) only slight reduction took place, but these have been considered positive in the light of the changes occurring in the syphilitic zone; one of these (No. 28) gave a positive Wassermann reaction. This emphasis is given to the colloidal gold test because of its evident superiority over other tests as an index of central nervous system involvement in hereditary syphilis. Next in value are the Wassermann reaction and the presence of globulin, which are about equal in incidence, though not parallel. The Wassermann reaction, of course, is unique, in that, when positive, it establishes a definite diagnosis. The Lange reaction was positive in every fluid showing other evidence of pathologic change, and in many cases it was the only evidence.

The superior delicacy of the Noguchi test over the Nonne test for globulin was demonstrated in syphilitic fluids as in no other condition, for we are here dealing with small quantities of globulin in most cases.

Pleocytosis occurred only in those children showing more marked evidence of syphilis of the central nervous system both in the clinical and laboratory findings. It is of interest to note that in this series pleocytosis, globulin content, and the intensity of the colloidal gold reaction were parallel.

The clinical evidence of syphilitic involvement of the central nervous system was in direct proportion to the pathologic findings in the cerebrospinal fluid. This was particularly true of the intensity of the colloidal gold reaction. Practically all of the fluids giving a positive Lange were from children showing some degree of mental impairment. Several fluids giving typical paretic curves were from children with marked dementia.¹⁶ The five normal fluids were from children whose only evidence of syphilis was a positive Wassermann reaction on the blood and who were apparently normal in every way.

15. The changes in No. 95 were apparently due to some technical error. No. 97 had military tuberculosis, with some possibility of meningitis; unfortunately there was no opportunity for a second examination. The changes in No. 111 alone cause doubt as to the selective action of syphilitic fluids.

16. G. McD. (No. 10), apparently normal when this examination was made, showed mental deterioration while under observation.

TABLE 2.—TUBERCULOUS MENINGITIS

No.	Name	Cell Count	Globulin		Fehling's	Pernan-ganate Index	Lange	Wasser-mann Reaction	Remarks
			Noguchi	Nonne					
4	F. C.	160	++	++	±	4.1	$\pm\pm 12442\pm 00$	0	
6	R. C. H.	4	0	0	++	2.7	$\pm 1222\pm\pm 000$	—	
8	E. G.	140	++	++	0	4.0	$\pm\pm 1332\pm 000$	—	
9	A. W.	384	++	++	0	3.7	$\pm\pm\pm 2555100$	0	
12	A. B. H.	†	++	++	+	4.0	0000033320	—	
13	H. H.	254	++	++	0	4.1	000±455200	—	
15	L. H.	160	++++	++	0	3.4	0013444420	0	
19	W. J. McC.	57	++++	++	0	3.3	$\pm 12444\pm 000$	—	
27	F. S.	57	+	+	0	2.4	$\pm 24422\pm 000$	—	
30	B. W.	10	0	0	+	2.4	0235530000	—	
53	A. O.	130	++	+	0	3.5	0002332000	..	} Later
56	A. O.	135	++	+	0	3.6	0013443000	..	
69	E. K. *.	16	+	+	+	1.4	00±553±000	—	
89	J. F.	263	+++	++	±	3.1	0003444000	—	
100	B. E.	171	+++	++	+	2.9	1114444100	..	} Later specimens
105	B. B.	315	+++	++	±	2.8	2224444100	—	
109	B. B.	340	+	+	0	...	01233333300	—	

* In this case the diagnosis may be questioned, as further observation was prevented by the child's removal from the hospital.

† Cell count not made.

Only three fluids in this series were from young infants (Nos. 60, 82, 98) with acute manifestations of infantile syphilis, and all gave a positive Lange, although the spinal fluid Wassermann reaction was negative. This fact merely points to the possibility of central nervous system involvement, and it would hardly be justifiable to establish a diagnosis of hereditary syphilis, without the Wassermann reaction on the blood, as Grulee and Moody¹⁷ have concluded.

In fluids from fifteen patients with tuberculous meningitis precipitation of the colloidal gold occurred in every instance, the maximum color change occurring in the dilutions 1 to 80, 1 to 160 and 1 to 320 in most cases. Fourteen of the fifteen patients had at the time of the fluid examination, or developed later, typical clinical manifestations of tuberculous meningitis. The diagnosis was confirmed by the demonstration of tubercle bacilli in the cerebrospinal fluid in fourteen cases and by necropsy in ten of them. In most of the cases the diagnosis was fairly conclusive from the clinical signs and the cell and globulin content of the fluid at the first examination. Reduction of Fehling's solution occurred only in the early stages of the disease.

Three of these patients were seen at the very onset (Nos. 6, 30, 69). The cell counts were low and globulin was present in only one. Permanganate indexes were slightly increased in two and low in one. All three fluids caused a maximum reduction of the colloidal gold solution in the same dilutions as found for the rest of the series.

Further observations on early meningeal processes would be valuable, as these few observations suggest a typical zone reaction for tuberculous meningitis, which may be an aid to early diagnosis.

Seven fluids from cases of purulent meningitis gave the typical findings of this condition, namely, a high cell count and globulin content, and the causative organism was found in all but one. The permanganate indexes were all high and Fehling's solution was not reduced. In general the colloidal gold was reduced by the higher dilutions of the fluid, but the intensity of the reaction or the zone affected was not constant. Nos. 11 and 42 are included here because they were obtained shortly before the development of the typical meningitic changes in the fluid. It will be noted that No. 11 caused a reduction of the colloidal gold in the dilutions 1 to 80, 1 to 160, and 1 to 320, the zone suggestive of a tuberculous condition. Certainly it was indicative of a beginning meningeal process and this was borne out by the later developments.

Six fluids from four patients with acute anterior poliomyelitis were examined. Four of these, one from each patient, at the first examina-

17. Grulee and Moody: *Jour. Am. Med. Assn.*, 1913, lxi, 13; *AM. JOUR. DIS. CHILD.*, 1915, ix, 17.

TABLE 3.—PURULENT MENINGITIS

No.	Name	Cell Count	Globulin		Fehl-ing's	Perman-ganate Index	Lange	Wasser-mann Reaction	Remarks
			Noguchi	Nonne					
1	F. H.	1,400	++	++	0	4.2	1 1 3 4 3 3 3 2 2 0	—	Streptococcus
2	S. M.	Pus	+++	+++	0	7.6	0 0 ++ 1 2 4 5 5	—	Meningococcus
11	W. B.	14	0	0	+	2.6	0 ++ 5 5 1 + 0 0	0	Abscess of brain; later, meningitis
14	W. B.	8,000+	+++	++	0	6.3	0 0 + 1 2 4 5 5 +	—	Staphylococcus
42	E. A.	3	0	0	+	2.5	0 ++ + 0 0 0 0 0 0	—	Mastoiditis
46	E. A.	6,000	++++	+++	0	6.1	1 2 0 0 0 3 4 4	—	Later fluid, meningitis staphylococcus
51	T. H. B.	Pus	++	++	0	4.2	0 0 1 3 4 5 4 3 3 3	—	Cause not determined
55	L. G.	6,000	+++	+++	0	4.3	0 0 0 2 2 3 3 4 4	—	Pneumococcus
107	G. W.	3,000	+++	++	0	3.7	0 0 0 1 1 3 3 3 3	—	Meningococcus

TABLE 4.—ACUTE ANTERIOR POLIOMYELITIS

No.	Name	Cell Count	Globulin		Fehl-ing's	Perman-ganate Index	Lange	Wasser-mann Reaction	Remarks
			Noguchi	Nonne					
44	H. F.	4	0	0	+	2.7	2 2 4 3 2 1 0 0 0 0	0	One week later
47	H. F.	4	0	0	+	2.1	1 1 1 + 0 0 0 0 0 0	—	
68	A. I.	25	+	0	++	2.6	2 2 3 4 4 4 1 0 0	—	
70	P. D.	9	+	0	++	2.0	0 + 3 4 2 0 0 0 0 0	0	One week later
79	S. W.	16	+	0	++	2.9	3 3 3 3 + 0 0 0 0 0	0	
85	S. W.	6	0	0	++	2.2	0 0 0 0 0 0 0 0 0 0	—	

TABLE 5.—MISCELLANEOUS PATHOLOGIC FLUIDS

No.	Name	Cell Count	Globulin		Fehling's	Permanganate Index	Lange	Wassermann Reaction	Remarks
			Noguchi	Nonne					
58	H. F.	16	++++	+++	0	9.7	0 0 0 0 ± 1 2 4 4 5	—	Golden yellow color
59	H. F.	42	++	0	±	2.8	4 4 3 2 2 0 0 0 0 0	0	Ventricle fluid clear, colorless same day
73	H. F.	3	+	0	+	2.4	2 3 3 3 ± 0 0 0 0 0	—	Two weeks later clear, colorless lumbar puncture fluid
72	C. M.	2	±	0	++	2.3	1 2 4 4 2 0 0 0 0	0	Mongolian Idiocy
112	R. C.	686	+	+	++	1.8	1 1 2 2 1 0 0 0 0	0	
115A	R. C.	330	+	0	1 1 2 2 2 0 0 0 0	—	Encephalitis; second and third fluids eight and ten days later
115B	R. C.	310	+	+	++	...	1 2 2 3 3 1 0 0 0	—	
90	C. F.	6	0	0	++	2.7	0 0 1 1 0 0 0 0 0	0	Hydrocephalus, brain tumor?
93	C. F.	1	0	0	++	...	± 1 2 2 2 0 0 0 0 0	—	
108	C. F.	3	0	0	++	...	1 2 2 2 1 0 0 0 0	—	
99	J. H.	2	0	0	++	...	± 2 3 4 4 4 1 ± 0 0	—	Mastoiditis; abscess of brain? Septicæmia; no necropsy
117	J. H.	6	++	2.2	1 2 3 3 3 0 0 0 0	—	

tion caused a reduction of the colloidal gold in the so-called syphilitic zone. Two of these showed pleocytosis and three gave positive globulin tests. In two cases (Nos. 47 and 85) fluids were examined after acute symptoms had subsided. In one, slight reduction took place in the lower dilutions, but the other was quite negative. Globulin was not present at the second examination. Wassermann tests made on the blood and cerebrospinal fluid of three of the four patients were negative. This occurrence of an early transitory reaction in the syphilitic zone in the acute stage of anterior poliomyelitis suggests an important aid in the diagnosis of this disease.

Table 5 is a group of fluids which gave evidence of pathologic change by one or more tests. The color changes were in this group almost entirely in the lower dilutions. No. 58 contained a large amount of globulin and albumin and had a golden yellow color. The ventricular fluid (No. 59) from the same patient was clear and colorless. The child recovered and the nature of the meningeal process was not definitely ascertained, although the clinical condition was suggestive of anterior poliomyelitis.

Fluids from R. C. (Nos. 112 and 115 A and B) were remarkable for the high cell count occurring with a small amount of globulin. In the absence of other definite findings, the condition was thought to be one of encephalitis. In the patient C. F. (Nos. 90, 93, 108) necropsy revealed no cortical or meningeal process which would account for the change in the cerebrospinal fluid, though hydrocephalus was definite.

It will be noted that a number of conditions giving obscure fluid changes all reduced the colloidal gold in the syphilitic zone; in some instances this was the only pathologic finding. The blood in these cases gave negative Wassermann reactions, and therefore they may be considered nonsyphilitic. This gives further support to the view mentioned above, that the term "syphilitic zone" is misleading and inaccurate.

In Table 6 are recorded the results of the examination of a number of clinical conditions in which the spinal fluid findings are quite normal.

Cases with meningismus showed no pleocytosis except in one instance (No. 106). All reduced Fehling's solution. The permanganate indexes were low in general, but were too variable to be significant.

It is noteworthy that fluids from epileptics and from nonsyphilitic mental defectives gave no evidence of any pathologic change by any of these tests. Fluids from patients with chorea gave normal findings, including negative Lange tests. In view of the fact that a large number of conditions gave positive Lange tests with no other pathologic findings, and that many of these latter proved to be the result of meningeal inflammation, it seems conclusive that these conditions

TABLE 6.—MISCELLANEOUS

No.	Name	Cell Count	Globulin		Feh- ling's	Perman- gnate Index	Lange	Wasser- mann Reaction	Remarks
			Noguchi	Nonne					
5	L. G.	5	0	0	++	2.0	0++± 0 0 0 0 0 0 0	—	Lobar pneumonia
26	E. G.	8	0	0	++	...	0 0 0 0 0 0 0 0 0 0 0	—	Lobar pneumonia, meningismus
74	D. L.	4	0	0	+	1.8	0 0 0 0 0 0 0 0 0 0 0	—	Lobar pneumonia, meningismus
84	D. P.	4	0	0	+	2.1	0 0 0 0 0 0 0 0 0 0 0	—	Bronchopneumonia, meningismus
106	M. MeD.	43	0	0	++	1.6	1 2 0 0 0 0 0 0 0 0 0	0	Otitis media, meningismus
116	S. L.	1	0	0	++	2.0	1 1 0 0 0 0 0 0 0 0 0	—	Pyelitis, meningismus
118	E. S.	1—	0	0	++	2.4	0 0 1 0 0 0 0 0 0 0 0	—	Lobar pneumonia, meningismus
35	J. L.	4	0	0	++	1.9	0±± 0 0 0 0 0 0 0 0 0	—	Chorea
40	H. P.	10	0	0	++	2.0	0±± 0 0 0 0 0 0 0 0 0	—	Chorea
104	R. R.	5	0	0	++	1.9	0 1 2 0 0 0 0 0 0 0 0	—	Chorea
37	P. W.	2	0	0	++	2.0	0 0 0 0 0 0 0 0 0 0 0	—	Mental deficiency
48	E. B.	3	0	0	++	2.1	0 0 0 0 0 0 0 0 0 0 0	—	Mental deficiency
49	E. B.	2	0	0	+	2.2	0 0±± 0 0 0 0 0 0 0 0 0	—	Mental deficiency
67	W. R.	5	0	0	+	2.7	0 0 0 0 0 0 0 0 0 0 0	0	Mental deficiency
75	G. G.	5	0	0	+	2.3	0 0 0 0 0 0 0 0 0 0 0	0	Mental deficiency
86	M. W.	2	0	0	++	2.2	0 0 0 0 0 0 0 0 0 0 0	0	Mental deficiency
39	J. B.	1	0	0	+	2.2	0±±± 0 0 0 0 0 0 0 0 0	0	Epilepsy
65	C. S.	2	0	0	+	2.5	0 0 0 0 0 0 0 0 0 0 0	0	Epilepsy

83	A. P.	6	0	0	++	2.2	0 0 0 0 0 0 0 0 0 0	0	Epilepsy
88	A. B.	2	0	0	++	1.9	0 0 0 0 0 0 0 0 0 0	0	Epilepsy
103	A. D.	4	0	0	++	1.8	0 0 0 0 0 0 0 0 2 0	0	Epilepsy
113	L. M.	5	0	0	++	1.4	1 1 0 0 0 0 0 0 0 0	0	Epilepsy
20	C. W.	3	0	0	++	2.3	0 0 0 0 0 0 0 0 0 0	—	Tuberculous bronchial glands
21	H. S.	3	0	0	++	2.2	0 0 0 0 0 0 0 0 0 0	—	Pulmonary tuberculosis
22	C. H.	2	0	0	++	1.8	0 0 0 0 0 0 0 0 0 0	—	Pulmonary tuberculosis
23	R. P.	6	0	0	++	2.5	0 0 0 0 0 0 0 0 0 0	—	Tuberculous bronchial glands
24	C. D.	4	0	0	++	2.4	0 0 0 0 0 0 0 0 0 0	—	Pleurisy, effusion
38	G. S.	3	0	0	++	1.9	$\pm\pm$ 0 0 0 0 0 0 0 0	—	Tuberculous
41	K. L.	3	0	0	++	2.3	0 0 0 0 0 0 0 0 0 0	—	Pulmonary tuberculosis
31	M. B.	2	0	0	++	2.0	$\pm\pm\pm$ 0 0 0 0 0 0 0 0	..	Malaria
32	T. B.	3	0	0	++	1.9	0 0 0 0 0 0 0 0 0 0	..	Malaria
33	C. B.	1—	0	0	++	2.2	0 0 0 0 0 0 0 0 0 0	..	Malaria
7	M. B.	8	0	0	+	2.1	$0\pm 1 2\pm$ 0 0 0 0 0 0	..	Status lymphaticus
34	D. C.	2	0	0	++	1.9	$0\pm\pm\pm$ 0 0 0 0 0 0	..	Nephritis
45	J. H.	4	0	0	+	1.9	0 0 0 0 0 0 0 0 0 0	..	Hydrocephalus
54	H. N.	6	0	0	+	2.2	0 0 0 0 0 0 0 0 0 0	..	Tetanus
43	W. K.	1—	0	0	++	2.1	0 0 0 0 4 0 0 0 0 0	..	Purpura
63	L. W.	10	\pm	0	+	2.1	0 0 0 0 0 0 0 0 0 0	..	Spastic quadriplegia
78	M. K.	4	0	0	++	2.1	0 0 0 0 1 5 3 1 0 0*	..	Septicemia

* Probably due to some technical error. No meningeal lesion revealed at necropsy.

affecting the nervous system, and having normal cerebrospinal fluids, are not meningeal in origin, neither are the meninges in any way affected.

SUMMARY

1. As an index of pathologic change in the cerebrospinal fluid, the colloidal gold reaction is more delicate than any other test here employed. A positive Lange reaction may be considered sufficient evidence of a pathologic process affecting the cerebrospinal nervous system, though the fluid in question is negative to all other tests. A normal fluid causes no reduction of the colloidal gold.

2. The presence of globulin in the cerebrospinal fluid, as determined by the tests of Noguchi and Nonne, is indicative of an inflammatory process, but is of no specific import. A negative globulin test may occur in a pathologic fluid.

3. The quantitative estimation of organic substances by the reduction of tenth-normal potassium permanganate shows such wide variations in normal fluids and those with slight pathologic change that it has no value as a diagnostic measure.

4. The qualitative presence of dextrose in the cerebrospinal fluid as determined by the reduction of Fehling's solution is of little value in the diagnosis of lesions of the central nervous system.

5. The specific diagnostic import of a given test is dependent on the character of the process causing the change in the fluid examined. Thus the cell content and bacteriologic findings are final in purulent and tuberculous meningitis. In the colloidal gold test the characteristic syphilitic zone reaction in hereditary syphilis is sufficient to establish the actual or potential existence of a syphilitic involvement of the central nervous system. This statement presumes a positive Wassermann reaction on the blood.

6. A number of affections give this same reaction, particularly acute anterior poliomyelitis, and no specific significance can be attached in nonsyphilitic cases.

7. The occurrence of a typical zone reaction in the colloidal gold test on fluids from patients with tuberculous meningitis is probable, and may be of value in diagnosis in the early stages. The occurrence of a transitory reaction in the lower dilutions suggests an aid in the diagnosis of acute anterior poliomyelitis.

SOME EARLY SYMPTOMS SUGGESTING PROTEIN SENSITIZATION IN INFANCY*

B. RAYMOND HOOBLER, A.M., M.D.

DETROIT

Through the painstaking researches of a great number of workers, we have come into possession of much information concerning the action of foreign protein when injected into animals subcutaneously, intraperitoneally or intravenously. The forms of protein most carefully studied are those of the various serums and the incentive for this study had its origin in the revolutionary discoveries of von Behring, Ehrlich, Wassermann, Abderhalden, Wright, Vaughan and a host of other workers. The study of the protein of the various serums led naturally to the study of the protein of the common food products, and out of this has come a great mass of information concerning the protein of milk, egg, meat and cereals. The leaders in the researches are Besredka, Vaughan, Osborn, Anderson and many others. Out of the tremendous amount of work which has been done in an effort to explain the phenomenon of anaphylaxis there have accumulated many facts which seem to be of such importance that they should be transported from the realm of the laboratory and made to serve the clinician in his daily work.

Two members of our society stand out pre-eminently in their efforts to bring to practical use the findings of the laboratory. Dr. Talbot¹ has shown the causal relation between egg protein and asthma; Dr. Schloss² has made clear through his researches that certain forms of infantile eczema are related to protein. It was thought for a long time that protein in order to enter the blood stream or body tissues unaltered must be introduced through the skin (subcutaneously, intraperitoneally, intramuscularly) or intravenously, but researches have been so abundant and conclusive during the past few years as to leave us no longer in doubt that a foreign protein, even when taken by mouth, may escape digestion and some of it be absorbed into the blood stream unaltered. The pioneers in this work were Ganghofer and Langer,³ Lawatschek,⁴

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* From the Children's Free Hospital of Detroit.

1. Talbot, F. B.: Boston Med. and Surg. Jour., clxxi, 695.

2. Schloss, O. M.: AM. JOUR. DIS. CHILD., 1912, iii, 341.

3. Ganghofer and Langer: München. med. Wchnschr., 1904, li, 1497.

4. Lawatschek: Prag. Med. Wchnschr., 1914, xxxix, 185.

Ascell,⁵ Moro,⁶ Rosenau and Anderson⁷ and Lust.⁸ The latest and most convincing researches have just been published by Schloss and Worthen.⁹ These workers have demonstrated beyond a question that absorption of protein occurs through the alimentary tract, particularly in those exhibiting signs of nutritional or gastro-enteric disorders. They state: "In gastro-enteric disorders, the mucous membrane becomes permeable, the degree of permeability being in direct ratio, apparently, to the severity of the disorder." My own researches in support of the proof of the absorption of milk protein into the blood stream unaltered are based on anaphylactic reactions in guinea-pigs.

The technic followed was that advised by Vaughan. Blood was collected from infants and children one hour after a feeding which contained milk protein in the usual quantity fed children of such ages. The blood was collected in citrate solution and taken to the laboratory and from 3 to 5 c.c. were injected intraperitoneally into normal guinea-pigs weighing about 250 gm. After suitable time had elapsed (at least 11 days), an injection of 5 c.c. of milk was also made intraperitoneally.

Blood was taken from normal children as well as from those with eczema, malnutrition and acute infections. The work, though still incomplected, confirms the work just published by Schloss and Worthen. Patients with eczema and malnutrition show undoubted permeability of the alimentary tract by positive anaphylaxis tests in guinea-pigs.

Just what happens when the foreign protein is absorbed unaltered into the blood stream has been the subject of numerous researches and much discussion without unanimity, but all are agreed that the individual absorbing such protein behaves differently under certain conditions than an individual who has not received this unaltered protein into its body tissue. This change in behavior toward the foreign protein by the individual is characterized as sensitization, or allergy.

The symptoms caused by the action of body tissue and fluids on this foreign protein is of great interest, for it varies from the mildest disturbance to an explosion of such severity as to cause sudden death. A condition fraught with such far reaching consequences should command our best thought. It is therefore my purpose to attempt to collect some of the earliest signs and symptoms which are evident in the individual thus sensitized. In attempting to determine these symptoms I have studied the symptomatology of a large number of authentic sensitization cases reported in literature. I have also made extremely

5. Ascoll: München Med. Wchnschr., 1902, xlix, 398.

6. Moro, E.: München. Med. Wchnschr., 1906, liii, 214.

7. Rosenau and Anderson: Bull. Hyg. Lab., U.S.P.H.S., 1908, No. 45.

8. Lust: Jahrb. f. Kinderh., 1913, lxxvii, 244.

9. Schloss and Worthen: AM. JOUR. DIS. CHILD., 1911, ii, 342.

careful observations continuing from the time of birth on a considerable number of infants, who have later shown unmistakable signs of sensitization. Also, through the intelligent cooperation of mothers, I have collected a great deal of material concerning the early symptoms of protein sensitization.

A study of the symptomatology of acute anaphylaxis lays for us the groundwork of our suggested early symptomatology of "suppressed anaphylaxis." It might be well to get the picture of anaphylaxis both in guinea-pig and in man as described by Vaughan:¹⁰

When a sensitized guinea-pig receives a reinjection of the same protein to which it has been sensitized after a proper interval of time, certain characteristic and practically invariable symptoms develop in three stages. The first stage is that of peripheral irritation. The animal is excited and evidently itches intensely, as is shown by its attempts to scratch every part of its body that can be reached with its feet. The second stage is one of partial paralysis. The animal lies upon its side or belly, with rapid, shallow, difficult breathing. It is disinclined to move, and when urged to do so shows more or less incoordination of movement, and muscular weakness, with partial paralysis, especially observable in the posterior extremities, which it drags. Rarely the animal dies in this stage. The third, or convulsive stage, begins with throwing the head back at short intervals. The convulsions become general, more frequent and violent, and the animal, having reached this stage, usually dies in a convulsion or immediately following one. Expulsion of urine and feces is frequent in the convulsive stage. Recovery after reaching the convulsive stage is exceedingly rare. When this stage is not reached, recovery usually occurs, and is so prompt and complete that after a few hours, or at most by the next day, the animal cannot be distinguished from its perfectly healthy fellows.

When the homologous protein is injected into a man sensitized by disease or by previous treatments, symptoms develop promptly, often within a few minutes, usually within a few hours. The stage of peripheral irritation is characterized by the sudden appearance of a rash. The rashes that occur most promptly are urticarial or erythematous. The lips and tongue seem swollen, and often the backs of the hands are swollen. The individual becomes apprehensive, says that he cannot breathe, and falls into a state of more or less marked collapse. In extreme instances there is retching, and occasionally vomiting. The second stage, that of great muscular weakness, continues for a variable time and usually rapidly passes away. In rare instances speedy death results.

It will be seen that the symptoms of acute anaphylaxis in both animal and man may be divided into three groups: those relating to (1) the skin, those relating to (2) the upper and lower respiratory tract, and those relating to (3) the digestive system. The condition the symptoms of which we are attempting to give does not derive its impetus from a large quantity of foreign protein suddenly injected into the body tissue, as takes place in the production of acute anaphylaxis, but rather from the absorption of very small quantities every three or four hours, dependent on the interval of feeding. Naturally this slow and oft-repeated method of receiving the protein removes

10. Vaughan: *Protein Split Products in Relation to Immunity and Disease*, 1913, p. 245.

from the symptomatology the explosive character of the onset, but nevertheless the essential element, namely, the introduction of a foreign protein into the body tissues, should cause essentially the same symptoms, although such milder in form. Particularly is this true if we believe with Vaughan that the symptoms characterizing both acute and suppressed anaphylaxis are due to one and the same cause and differ only in intensity of reaction. Vaughan maintains that in the process of digestion of the protein parenterally the poisonous portion of the protein molecule is set free within the body tissues, and there being no well established protective mechanism, the symptoms of acute or suppressed anaphylaxis take place, dependent upon the quantity and the rapidity with which the poison is set free. Vaughan further states that daily injections of a protein tend to suppress the explosive character of anaphylaxis. This would be analogous to an infant who, being fed daily on milk, absorbed a small quantity of it into the blood stream, unaltered by reason of the permeability of the intestine.

When sufficient quantity of protein is absorbed unaltered, then sensitization takes place and later reaction occurs, not in the explosive character of acute anaphylaxis, but rather in the form of the symptoms of suppressed anaphylaxis; the early evidences of which divide themselves into five definite groups: (1) those relating to the skin; (2) those having to do with upper respiratory tract; (3) those involving the lower respiratory tract; (4) those connected with the digestive organs, and (5) those referred to the nervous mechanism. In addition to this group of symptoms, there is the important condition of family predisposition toward one or another form of protein. In a large percentage of cases under my personal observation it has been possible to learn of some form of sensitization in father, mother or grand parents. It usually shows as hay fever, rose colds, asthma, or distinct reaction to one or another form of food proteins, either egg, bean, oatmeal, milk, beef, fish. It is therefore of very great importance in our study of each case to determine whether or not we have to deal with an offspring whose parents have exhibited definite signs of sensitization.

Let us now consider the symptoms arranged according to the groupings just named. Perhaps the earliest manifestations of sensitization appear in the form of the various lesions of the skin. These may differ greatly in form and intensity. There may be the mildest erythema, either localized or general, or it may take the form of blotchy areas, often of very intense color. There may be urticaria, which may consist of a single wheal or be of the giant type or any degree between these forms. Usually the earliest forms are single urticarial wheals and are often considered by the mother the result of insect bites. There may be rashes, which are usually of the miliary type, and are found particularly about the neck and chest. This form is often thought to

be due to dressing the infant too warmly. In addition to these forms, there may be a mere roughening of the skin, without exposure, similar to chapping.

The whole group of skin lesions due to sensitizations have usually been classified as intestinal rashes. Empirically, they have been associated with food disturbances, but just how they have been brought about has been an open question. Indeed, even with our advanced knowledge, it is difficult to explain the mechanism.

The next common phenomena of sensitization are those connected with the upper air passages. They manifest themselves in diverse ways. There may be symptoms which originate from vasomotor disturbances in the mucosa of the upper air tract. These exhibit themselves in (*a*) sneezing, (*b*) snuffles, and (*c*) rubbing the nose.

Sneezing is often a persistent symptom, until the mother is thoroughly alarmed, believing that the baby is catching a cold. This, coupled with snuffles, which may be so severe that the baby may be forced to breathe through its mouth, constitutes what has been aptly called by mothers a "dry cold." Infants who have been subject to many colds, yet never show a discharge or any other pathologic lesion other than perhaps a rather turgid nasal mucosa, are, in most cases, manifesting one of the common early symptoms of protein sensitization. Rubbing the nose is quite a familiar activity of certain infants and compares with that symptom noted commonly in animals as one of the early accompaniments of anaphylaxis.

The symptoms relating to the respiratory tract are usually of much later occurrence than those of the upper air tract. They are (*a*) wheezing, (*b*) periods of increased respiration, and (*c*) cough.

Wheezing is a very outstanding symptoms and one which can be readily detected. The expressions that mothers often use are that the child "breathes heavily" or that it "wheezes in its chest." This, in some of my cases, has been a very early symptom and precedes the true asthmatic attack by months. When one listens to one of these wheezing chests he is disappointed in finding so few variations from normal. The changes consist chiefly in increased breath sounds with a prolonging of the expiratory portion. The symptom of increased respiration is at first without dyspnea, but later with some dyspnea. These appear quite a time before the true asthmatic attack occurs. A cough occurs in some children, simulating that of mothers' croup, for which there is no adequate pathologic explanation. The cough is often very persistent, but usually is of short duration and disappears as suddenly as it comes on.

The symptoms relating to the digestive system often appear in the presensitization period and consist of an acute digestive disturbance. This is followed later by occasional vomiting attacks, in which an entire

feeding may be ejected suddenly without any apparent cause. This vomiting is often accompanied by one or two urticarial wheals or by some one of the numerous skin manifestations.

The symptoms arising from some disturbance of the nervous system include the conditions generally described under the words irritable, restlessness, fretful and sleepless. Peripheral nerve irritability is very marked. It is most exasperating to watch an animal entering on an anaphylactic shock as it attempts to respond to the call of peripheral nerve endings. Something akin to this no doubt is experienced by an infant and produces for the time being periods of irritability, restlessness, and fretfulness. Sleeplessness is a rather frequent accompaniment of sensitization. Among several of my cases this was the outstanding characteristic and was the condition for the alleviation of which I was consulted.

General Characteristic of Symptoms: All of the above symptoms come and go with great rapidity. Not all of them occur together; often but one of them occurs and quickly disappears. Later on in the same child there is a different manifestation. As the sensitization becomes more marked, the symptoms increase in severity as well as in variety. If the food protein is constantly increased, as is usual in bottle-fed infants, the manifestations of sensitization appear more frequently, remain longer and are more intense; thus many transient erythemas and fine rashes become displaced by the more permanent eczema, which appears first only in a few spots, as on the cheeks, over the fontanel, and behind the ears. If protein is persistently increased, the eczema gradually spreads until the entire body surface may become involved.

In like manner the respiratory symptoms become more prominent. The wheezing is more marked, the breathing more labored and eventually the extreme manifestation appears in the form of an attack of asthma. It rather frequently happens that the extremes of both the skin and the respiratory manifestations occur in one and the same patient, in which case we have a child with severe eczema suffering from frequent attacks of asthma. The other symptom groups tend to become more manifest and the finished product of protein sensitization presents a distressing picture. Fortunately all the symptom groups do not tend to appear in the same child. Certain children appear to be more susceptible to the skin manifestations, while others will show only the upper air tract symptoms, while in others the respiratory symptoms predominate.

I have mentioned only those symptoms which occur early in the period of sensitization. Some of these symptoms persist throughout the lifetime of the individual. Others disappear in the early years of life.

The process by which one becomes immune is little understood, although it has been possible to produce immunity, as demonstrated by both Talbot and Schloss. The relation of protein sensitization to various nutritional disturbances has been referred to by Schloss and Worthen. In their summary they state that their "results demonstrate the possibility that certain nutritional disorders in artificially fed infants may be due to the biologic character of the food." This line of research is well worth continuing, since it has already been shown by Vaughan that marasmus is one of the terminal symptoms of suppressed anaphylaxis in rabbits which have received daily injections of a foreign protein.

I am well aware that many of the symptoms named are symptoms of other very common diseases, and it is not my desire to claim that they occur only as symptoms of protein sensitization; but it is my observation that when the group of symptoms as outlined occurs and reoccurs in an infant early in its existence, one should be on guard and should carefully watch for further developments.

Various tests may assist in diagnosis (*a*) blood examination for eosinophilia, (*b*) cutaneous skin reactions, (*c*) precipitin tests on urine, and (*d*) anaphylactic reactions. It is extremely important that this condition be recognized early, and when so recognized it need not go on to its extreme manifestation in the forms of eczema, asthma, malnutrition and, I have no doubt, many other nutritional disorders whose relation to protein sensitization have not yet been proved.

SUMMARY

1. I believe that permeability of the alimentary tract to unaltered protein in certain infants has been fully demonstrated.

2. The absorption of this unaltered protein produces a group of symptoms, mild at first, and later increasing in intensity, which I believe to be an expression of "suppressed anaphylaxis."

3. By early recognition of such cases, followed by proper food modifications, the symptoms may entirely disappear or be greatly ameliorated.

THE CREATININ AND CREATIN CONTENT OF THE BLOOD OF CHILDREN *

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AND

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There are comparatively few data on the creatin-creatinin content of the blood, as it was not until 1914 that a satisfactory method for its determination was devised by Folin.¹ At the same time Folin and Denis² reported the results of a number of determinations in adults with different clinical conditions. They found that the blood content of normal adults averaged a little over 1.1 mg. of creatinin per 100 c.c. They were unable to find any specific creatinin retention, but found an increased retention (over 20 mg.) in some cases of nephritis. About the same time Neubauer,³ in a paper on the use of creatinin as a test of renal function in nephritis, stated that creatinin retention in the blood was very high in some cases of nephritis, reaching 20 mg. per 100 c.c., and that normally it was present in quantities less than 1 mg. per 100 c.c. He gives no other figures.

In two more recent papers Myers and Fine⁴ and Myers and Lough⁵ report the result of some studies of the creatin-creatinin content of the blood in nephritis. They found, as Folin found, a high retention figure in some cases, but not in all. They noted that all their cases of nephritis with a retention of over 5 mg. of creatinin per 100 c.c. terminated fatally. Of these, there were eleven cases. In all they studied thirty nephritics. In only five patients was the retention under 2 mg. (normal values) and two of these died. From a clinical point of view they consider a case with a creatinin content between 3 and 5 mg. as having an unfavorable prognosis, and those with over 5 mg. as fatal. In a number of normal cases tested they found the creatinin content under 2 mg. per 100 c.c. of blood in almost every case.

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* From the Department of Pediatrics of the Washington University Medical School and St. Louis Children's Hospital.

* Read at the Twenty-Eighth Annual Meeting of the American Pediatric Society, held at Washington, D. C., May 8-10, 1916.

1. Folin: *Jour. Biol. Chem.*, 1914, xvii, 475.

2. Folin and Denis: *Jour. Biol. Chem.*, 1914, xvii, 487.

3. Neubauer: *München. med. Wchnschr.*, 1914, lxi, 857.

4. Myers and Fine: *Jour. Biol. Chem.*, 1915, xx, 391.

5. Myers and Lough: *Arch. Int. Med.*, 1915, xvi, 536.

The creatinin retention in nephritis is apparently but a part of the general retention of nitrogenous substances in the blood, which has been noted by many observers, and there is a definite parallelism between the creatin retention and the retention of the total nonprotein nitrogen, urea and uric acid. There is no evidence at hand leading one to consider it a more delicate index of retention than any of the other nitrogenous substances, and in fact it seems to be more easily excreted.

In the figures obtained by both of these groups of workers the creatin content varied widely and neither paper discusses the creatin figures. If one studies the tables of Folin and Denis it will be noted that the creatin content of the blood averages about 10 mg. per 100 c.c.

Because of the difference in the creatin-creatinin metabolism in adults and children, as measured by their content in the urine, we decided to test the blood of a number of children with different clinical conditions and compare the results with the total nonprotein nitrogen of the blood.

Folin and Denis⁶ found that the content of nonprotein nitrogen in the blood of a healthy adult was from 22 to 26 mg. per 100 c.c. Later they published determinations made in a large number of clinical conditions, which showed that there is a definite increase or retention of the nonprotein nitrogen in nephritics with uremia, and that greater variations are found in the blood of hospital patients. Slightly higher values are not necessarily associated with renal disturbance. These findings have been confirmed by a number of observers. There is an increase of from 4 to 6 mg. after a full meal, and usually a slight increase in acute infections. In nephritics the content may vary from normal to ten times normal, the high values being found in actual or impending uremia.

In children the nonprotein nitrogen content does not differ in any marked degree from the adult. Tileston and Comfort⁷ made determinations on fifty-one children with a variety of clinical conditions. Normal children gave values of from 20 to 34 mg. per 100 c.c. Only one case, that of a child with acute nephritis, showed a definitely increased value (63 mg. per 100 c.c.), and this later became normal with the disappearance of uremic symptoms. The rest of the observations were made on children with acute and chronic infections, in whom normal values (20 to 32 mg. per 100 c.c.) were found. In normal infants the nonprotein nitrogen content has been found to vary between 23 and 44 mg. per 100 c.c. by Schlutz and Pettibone,⁸ whose observations were made on nine infants from $\frac{1}{2}$ hour to 10 days old.

6. Folin and Denis: *Jour. Biol. Chem.*, 1913, xlv, 29.

7. Tileston and Comfort: *AM. JOUR. DIS. CHILD.*, 1915, x, 278.

8. Schlutz and Pettibone: *AM. JOUR. DIS. CHILD.*, 1915, x, 206.

TABLE 1.—NITROGEN RETENTION IN CHILDREN IN SCARLET FEVER AND VARIOUS CLINICAL CONDITIONS

Initials	Sex	Age, Years	Condition	Creatinin, C.e.	Nonprotein Nitrogen, C.e.	Creatin, C.e.
A. C.	♀	2	Normal.....	1.41	22.0	7.17
C. H.	♀	3	Normal.....	1.20	26.0	4.70
B. V.	♂	7	Normal.....	3.44	26.0	2.77
C. C.	♂	9	Normal.....	2.80	26.0	4.10
T. H.	♂	12	Normal.....	2.30	33.0	6.40
N. M.	♀	13	Normal.....	0.78	29.0	4.92
L. K.	♀	14	Normal.....	2.30	30.0	4.55
E. B.	♂	5	Normal.....	0.97	25.0	7.16
M. R.	♀	9	Normal.....	1.92	27.0	2.95
M. R.	♀	8	Normal.....	0.90	32.0	2.21
M. K.	♀	3	Normal.....	0.79	32.0	3.41
C. Z.	♂	8	Normal.....	2.70	31.0	2.60
H. Z.	♂	5	Normal.....	0.58	28.0	3.92
C. P.	♂	3	Normal.....	3.24	28.0	3.22
M. R.	♀	12	Normal.....	1.00	31.0	3.40
R. D.	♀	2	Normal.....	0.68	25.0	3.54
E. B.	♂	11	Scarlet fever (febrile): Severe.....	3.44	31.0	3.16
F. S.	♂	5	Mild.....	1.38	29.0	5.28
A. C.	♂	4	Severe.....	1.62	22.0	5.83
D. B.	♂	2	Severe.....	2.38	34.0	1.85
M. M.	♀	8	Mild.....	1.42	28.0	2.97
I. M.	♀	6	Mild.....	1.82	27.0	3.23
I. H.	♀	4	Mild.....	1.08	16.0
M. I.	♂	6	Mild.....	2.79	29.0	2.58
J. W.	♂	11	Mild.....	1.77	35.0	3.73
A. F.	♂	6	Mild.....	1.61	32.0	4.11
H. B.	♂	1½	Severe.....	3.82	26.4	4.12
O. B.	♂	3	Severe.....	2.03	21.5	3.91
A. M.	♀	5	Severe.....	2.32	29.0	3.14
B. S.	♀	4	Severe.....	1.91	21.0	2.62
I. F.	♂	4	Severe.....	3.00	25.0	2.38
L. M.	♀	12	Scarlet fever (afebrile): Early.....	1.87	19.0	5.67
A. F.	♂	2½	Early.....	1.43	30.0	3.84
M. E.	♀	3	Early.....	2.38	18.0	3.41
L. O.	♂	10	Early.....	2.12	19.0	4.06

TABLE 1.—NITROGEN RETENTION IN CHILDREN IN SCARLET FEVER AND VARIOUS CLINICAL CONDITIONS—(Continued)

Initials	Sex	Age, Years	Condition	Creatinin, C.c.	Nonprotein Nitrogen, C.c.	Creatin, C.c.
S. M.	♂	3	Scarlet fever (afebrile): Early.....	2.78	18.5	3.17
W. J.	♂	6	Early.....	2.20	33.0	3.68
E. W.	♂	4	Early.....	2.27	14.5	3.78
C. L.	♂	7	Early.....	2.36	30.0	2.51
G. N.	♀	8	Early.....	1.06	25.0	3.94
H. B.	♀	9	Early.....	1.33	23.0	2.29
J. W.	♂	11	Reexamined (3d week): “ “	1.34	32.0	4.51
A. F.	♂	6	“ “	1.28	20.0	4.85
M. I.	♂	6	“ “	2.80	29.0	5.53
H. B.	♀	9	“ “	1.62	22.5	4.63
G. N.	♀	8	“ “	1.21	21.7	3.97
I. M.	♀	6	“ “	1.44	24.0	4.06
M. M.	♀	8	“ “	1.27	22.4	3.44
I. H.	♀	4	“ “	0.62	27.0	4.80
C. L.	♂	7	“ “	0.94	21.6	3.22
H. C.	♂	5	“ “	1.90	22.3	3.41
F. S.	♂	5	“ “	1.00	24.5	4.21
M. S.	♀	9	Congenital heart disease: Pulmonary stenosis.....	0.99	33.0	2.80
F. B.	♂	1	Pulmonary stenosis.....	0.74	29.0
R. R.	♀	8	Chorea.....	2.50	26.0	4.50
Mc. G.	♂	9	Typhoid conv.	3.22	30.0	4.53
R. C.	♂	3	Nephritis: Acute.....	1.46	23.0
M. D.	♀	3	Chronic diffuse.....	2.52	42.0	7.20
L. V.	♂	3	Chronic diffuse.....	2.07	20.0
K. P.	♂	1½	Acute (mild).....	1.21	36.0	5.28
V. R. 1/17....	♀	6	Acute (severe).....	0.80	39.0
V. R. 1/28....	Severe.....	1.66	49.0
V. R. 3/15....	Severe.....	1.77	18.0
V. R. 4/8....	Severe.....	0.98	21.7
R. K.	♂	11	Tuberculosis, open pulmonary..	1.67	23.0	10.00
L. O. N.	♂	13	Tuberculosis, open pulmonary..	0.71	32.0	5.00
L. S.	♀	6	Tuberculosis, open pulmonary..	1.40	35.0	5.50
M. S.	♀	5	Tuberculosis, open pulmonary..	1.78	40.0	3.68
M. H.	♂	14	Anemia, malarial.....	0.83	49.0	6.74

TABLE 1.—NITROGEN RETENTION IN CHILDREN IN SCARLET FEVER AND VARIOUS CLINICAL CONDITIONS—(Continued)

Initials	Sex	Age, Years	Condition	Creatinin, C.c.	Nonprotein Nitrogen, C.c.	Creatin, C.c.
W. P.	♂	11	Anemia, secondary.....	1.54	25.8
M. B.	♀	10	Myocarditis.....	0.76	24.0	4.78
L. C.	♂	8	Cardiac decompensation.....	3.20	29.0	2.20
H. S.	♀	9	Chronic bronchitis.....	1.60	24.0	2.25
M. N.	♀	7	Chronic bronchitis.....	1.71	40.0	4.53
S. F.	♂	1	Chronic bronchitis.....	1.49	32.0	4.15
H. K.	♀	½	Chronic malnutrition.....	2.85	20.0	3.00

The methods used in our study were those of Folin and Denis⁹ for the nonprotein nitrogen and of Folin¹ for the creatin and creatinin. In the latter test the blood was laked in distilled water before shaking with picric acid, instead of being laked in a saturated solution of picric acid. Five c.c. of blood were used in determining the nonprotein nitrogen (N. P. N.) and 6 c.c. for the creatinin (Cr.₁) and creatin (Cr.₂) determinations. All figures are for milligrams in 100 c.c. of blood.

Determinations were made on seventy-five children. Many of these, particularly those with scarlet fever, were tested a number of times. In order to avoid any factor which might result from the ingestion of food, the blood for the tests was taken early in the morning before the children were given their breakfast, and thus about twelve hours after the last meal. The children were placed on a creatin-free diet for the study. In Table 1 the results in seventy-seven tests are tabulated. The cases are grouped into normals; scarlet fever at the time of exanthem, when there was an elevation of temperature; afebrile scarlet fever, in the first week; and a number of examinations made in the third week of convalescence (negative urinary findings). In addition a number of miscellaneous conditions are added.

The creatinin figure for normal children varies between 0.58 and 3.44 mg. per 100 c.c. In ten children the figure was under 2 mg., and in two above. The febrile scarlet fever cases varied between 1.08 and 3.82 mg., but with half above 2 mg. and none under 1. The highest figure in an early afebrile case was 2.78, but in half the cases the content was a little over 2 mg. In convalescence only one case in eleven had a content above 2 mg. Like variations were encountered in the miscellaneous conditions. There was no specific retention in any of our cases, although as a whole the figure for the creatinin content of the

9. Folin and Denis: Jour. Biol. Chem., 1912, xi, 527.

blood in children is somewhat higher than that for the adult. A comparison of the creatinin content with the nonprotein nitrogen is briefly shown in Table 2, in which the cases are grouped according to the amount of each present.

Under 30 mg. of nonprotein nitrogen and 2 mg. of creatinin are considered as corresponding to average normal figures and hence are grouped together. In Group 2 are cases with a figure of from 30 to 35 mg. of nonprotein nitrogen and from 2 to 3 of creatinin per 100 c.c.; Group 3, from 35 to 40 of nonprotein nitrogen and from 3 to 4 of creatinin; Group 4, over 40 mg. of nonprotein nitrogen and 4 of creatinin.

TABLE 2.—COMPARISON OF CREATININ AND NONPROTEIN NITROGEN CONTENT IN VARIOUS CLINICAL CONDITIONS

	Group 1		Group 2		Group 3		Group 4	
	Non-protein Nitrogen	Creatinin	Non-protein Nitrogen	Creatinin	Non-protein Nitrogen	Creatinin	Non-protein Nitrogen	Creatinin
Normal.....	11	10	5	4	..	2
Scarlet fever.....	11	8	4	4	..	3
Scarlet fever (afebrile).....	17	14	4	7
Tuberculosis.....	1	4	2	..	1	..
Nephritis.....	2	3	..	3	2	..	2	..

In addition, the nonprotein nitrogen and creatinin were both in Group 2 in two cases each of congenital and of chronic valvular heart disease and in a case of myocarditis. In a child with secondary anemia and in one who had been starved for two days the nonprotein nitrogen was high (over 40), while the creatinin was low. In a typhoid convalescent, in a child with cardiac decompensation and in one with chorea the creatinin figure was in a higher group. As a rule both the nonprotein nitrogen and the creatinin were within the same general limits as have been found for normal adults, and as Tileston found for the nonprotein nitrogen in children, although as a whole the average figures for both are a little higher in children.

We have been able to study but six cases of nephritis. The retention figures in these were not high and but one case was fatal (not uremic). As noted in Table 1 the nonprotein nitrogen was not increased in two cases and the creatinin was normal in three. In one case with a low nonprotein nitrogen figure the creatinin was high and in

two an opposite condition held. As the nephritis in a given case subsides the amount of retention decreases, as illustrated by the case shown in Table 3.

TABLE 3.—DECREASE OF NITROGEN RETENTION WITH SUBSIDENCE OF NEPHRITIS

Date	Non-protein Nitrogen	Creatinin	Creatin
1/17/16.....	39	0.80	5.45
1/28/16.....	49	1.66	4.55
3/15/16....	18	1.77	4.61
4/ 8/16.....	22	0.97	5.15

A number of cases of scarlet fever were followed from the stage of the acute exanthem until desquamation was completed and tests made weekly for five weeks. None of the fourteen cases followed developed a typical postscarlatinal nephritis in the third or fourth week. After the acute febrile period was over, there was usually a slight fall in the nonprotein nitrogen and creatinin, although in the second week a few showed a slight increase. One severely toxic patient, who died in the third week, showed an increasing retention. The kidney in this case showed acute fatty degeneration.

TABLE 4.—INCREASING NITROGEN RETENTION WITH PROGRESSIVE POSTSCARLATINAL NEPHRITIS

	Nonprotein Nitrogen	Creatinin
First week.....	28	1.51
Second week.....	34	2.38
Third week.....	47

Although as stated there was no discussion of the creatin figures in the earlier papers, a study of Folin's tables shows that in a general way the creatin of the blood of adults averages about 10 mg. per 100 c.c. There is no apparent relationship between the amount of creatin and creatinin. We found much less creatin in the blood of children, rarely over 5 mg. per 100 c.c., and the figure for the total creatin-creatinin was rarely over 6 mg. This is interesting in view of the fact that creatin is found in the normal urine of children and is not present in the urine of adults. We have been unable to find any specific relationship in our figures between the creatinin and creatin, or any relation

between the amount of creatin and the clinical condition. There is no definite relation between the total nonprotein nitrogen and the creatinin-creatin content.

A few experiments were made to observe the influence of certain factors on the nonprotein nitrogen and creatinin content. In one the effect of copious water drinking to flush the kidneys was tried. A fixed diet was given for six days. On the first three days but 200 c.c. of water was allowed, on the fourth and fifth, 2,000 c.c. and on the sixth day 3,000 c.c. Determinations were made on the morning following the last five days. The effect was negligible, as is shown by the figures in Table 5.

TABLE 5.—EFFECT OF COPIOUS WATER DRINKING ON NITROGEN RETENTION

Water Daily, C.c.	Nonprotein Nitrogen	Creatinin	Creatin
200.....	28.0	1.18	3.38
200.....	23.8	2.00	3.24
2,000.....	25.7	1.41	3.60
2,000.....	26.0	1.33	3.42
3,000.....	22.5	1.15

Determinations were also made on a child who was being starved for other purposes. A slight increase in the content of all three substances was observed during the period of starvation. An increased creatinin excretion in the urine occurs during starvation.

TABLE 6.—EFFECT OF STARVATION ON NITROGEN RETENTION

Day	Diet	Nonprotein Nitrogen	Creatinin	Creatin
1	Regular.....	31	1.39	4.86
2	Starvation.....	34	1.67	3.97
3	Starvation.....	35	1.70	6.70
4	Regular.....	31	1.36	4.10
5
6	Regular.....	..	1.24	3.56

Several children were placed on a fixed creatin-free diet for six days and analysis of both the urine and blood made daily after the second day. The figures obtained in two cases are given in Table 7.

In the first case both the absolute and relative (percentage relation to total nitrogen) amount of creatinin of the blood varied considerably, while in the second it is quite uniform. In the first case, as in others, there seems to be no definite relationship between the creatin of the blood and of the urine, or between the quantities of total creatin-creatinin.

TABLE 7.—NITROGEN CONTENT OF BLOOD AND URINE ACCOMPANYING CREATIN-FREE DIET

Blood, Mg. N per 100 C.c.			Urine, Total N		
Nonprotein	Creatinin	Creatin	Total Nitrogen Grams	Creatinin Mg.	Creatin Mg.
L. O'N.*					
17.8	0.84	4.60	7.32	541	59
21.9	0.67	3.78	5.82	476	12
22.1	1.90	4.70	5.46	379	82
22.8	1.46	4.57
21.5	2.04	3.52	6.67	542	83
W. P.†					
26.7	1.33	3.54	330	95
25.8	1.54	3.24	312	123
21.3	1.54	3.72	333	270
27.0	1.25	3.63	381	206

* Fourth week of mild scarlet fever.

† Secondary anemia.

The second case is given to show the very slight daily fluctuation of creatinin sometimes observed. What mechanism controls the relation between the amount in the blood and the quantity of the urine we were unable to ascertain. The amount of creatin-creatinin to total nonprotein nitrogen in 100 c.c. of blood is much greater than the proportion of creatinin to total nitrogen of the urine.

THE ENERGY METABOLISM OF A CRETIN *

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Studies of the glands of internal secretion have shown that the thyroid gland has a very profound effect on the energy metabolism. An overproduction of the active element of the gland increases the irritability of the nervous apparatus and raises the metabolism, while an underproduction reduces the irritability of the nervous system and lowers the metabolism. The former symptoms are shown clinically in exophthalmic goiter and the latter in myxedema and cretinism.¹

Magnus-Levy² established the fact that in exophthalmic goiter the energy requirements were greatly increased, being from 50 to 70 per cent. above the normal, and that in myxedema and cretinism³ the heat production might be as low as 45 to 50 per cent. below the normal. Du Bois⁴ reported briefly the results of his researches in Professor Lusk's laboratories, in which he studied the diseases of the thyroid gland and obtained similar results to those of Magnus-Levy. Du Bois says:

In one cretin who was 36 years old, but had the mental and physical development of a child of 8, the total energy requirement was from 18 to 25 per cent. below the normal, but was raised almost to the normal on the third day of treatment with thyroid extract.

The boy, C. G., who was studied in this investigation, entered the children's ward of the Massachusetts General Hospital, Jan. 18, 1915, aged 3 years and 8 months. He was born at full term, and it was necessary to use artificial respiration for ten minutes before he breathed. His parents said he weighed 14 pounds at birth. He was breast fed entirely for one year. During the second year he was given whole milk and crackers, and after that cereals and bread were added to the diet. He was unable to feed himself, could not speak any words, and was unable to sit up alone. His parents thought that he recognized them. The physical examination showed a stupid, well-nourished, fat child, with very little musculature, lying in bed with a blank facial expression. He was phlegmatic and remained quiet most of the time, but when he cried, his voice was hoarse. The hemoglobin was 70 per cent. The skin was pale, sallow, dry, thickened, and wrinkled. The hair was coarse, bristly and dry. The anterior fontanel, though closed, still showed a depression. The tongue was thick, and protruded from the mouth most of the time. The extremities were shorter than normal; the hands square and thick, the skin

* Submitted for publication May 17, 1916.

* From the Nutrition Laboratory of the Carnegie Institution of Washington, and the Children's Medical Department, Massachusetts General Hospital.

1. Lusk: *Science of Nutrition*, Ed. 2, Philadelphia and London, 1909, p. 268.

2. Magnus-Levy: *Berl. klin. Wchnschr.*, 1895, xxxii, 650.

3. Magnus-Levy: *Ztschr. f. klin. Med.*, 1904, lii, 201.

4. Du Bois: *Jour. Am. Med. Assn.*, 1914, lxiii, 827.

over them being wrinkled. There was a slight umbilical hernia, and there were marked supraclavicular pads of fat. Otherwise the physical examination was normal, except for a systolic murmur heard over the whole precordia. He was the typical picture of a cretin, with the mental development about that of a four to six months old infant. His weight on entrance was 11,800 gm.

His energy metabolism was studied after feeding, in the apparatus furnished by the Nutrition Laboratory of the Carnegie Institution of Washington.⁵

Since he was larger than the infants for which the chamber had been planned, there was very little room to spare after he was in it. This, however, did not seem to bother him during the first observations,



Fig. 1.—Metabolism of cretin, C. G.

on January 19, when two very quiet periods were obtained, and are marked with a star in Table 1 as minimum periods. On January 30, after a course of ten days' treatment with thyroid extract, he had improved very markedly, showed more intelligence, became more active, and showed signs of discomfort in his restricted quarters. He was relatively very active and it was impossible, unfortunately, to get minimum periods for comparison after he was treated.

5. The technic has been previously described by Benedict and Talbot: *Carnegie Publication* 201, 1914, p. 32.

The lack of data of the metabolism of normal children makes comparisons of the metabolism of C. G. less satisfactory. Table 2, however, is given to show his metabolism compared to two healthy infants, one of which was aged $8\frac{1}{2}$ months, and the other 10 months.

TABLE 1.—ENERGY METABOLISM OF C. G., CRETIN

Date, 1915	Body Weight and Surface	Height, Cm.	Heat Produced per 24 Hours, Calories			Average Pulse Rate	Relative Activity
			Total	Per Kilo-gram	Per Square Meter Lissauer		
Jan. 19	11.83 Kg. $10.3 \sqrt{w^2} = 0.535$ sq. m.	85	460†	94	Quiet
			464	39	567*	95	Quiet
			497	42	929*	95	Very active
			616	52	1,151	116	
Jan. 30	10.78 Kg. $10.3 \sqrt{w^2} = 0.503$ sq. m.	85	672	119	Very active
			725	67	1,441	127	Very active

* Minimum periods of heat production, pulse and activity.

† Preliminary period, not used in calculations.

TABLE 2.—COMPARISON OF METABOLISM OF THE CRETIN C. G. WITH THAT OF TWO NORMAL INFANTS

Name	Age	Body Weight Without Clothing	Height, Cm.	Heat Produced per 24 Hours, Calories		
				Total	Per Kg.	Per Sq. M. Body Surface, Lissauer
Normal Infants:						
R. L.	8½ mos.	7.58	71	455	59	1,140
E. G.	10 mos.	9.37	74	480	51	1,046
Creatin, C. G. ...	3 yrs. 8 mos.	11.83	85	479*	40½*	808*

* Average of two quiet periods.

Table 2 is given for comparison because there are no available figures of normal children during the fourth year of life. It is obviously valueless to compare C. G.'s metabolism with that of the adult or with that of Du Bois' 36-year-old cretin. One might speculate as to how the metabolism of C. G. would compare with that of an infant of his own age. In place of that, Table 2 is given as the most available substitute.

The total metabolism for twenty-four hours of these three babies was not very far apart. The comparison of the metabolism per square meter of body surface and per kilogram of body weight is of greater importance since it shows that in both instances the metabolism of the cretin is at least 25 per cent. lower than that of the two infants. Since the cretin was a fat, phlegmatic individual, who did not move much, one would expect that his metabolism would be lower than that of a well-muscled, active baby.⁶ It is evident that he was living on a very low plane and that his energy metabolism was considerably lower than what one would expect for a child of his age. These results, while inconclusive, because of the scarcity of material for comparison, are consistent with the findings of Du Bois and others.

6. Talbot: The Energy Metabolism of an Infant with Congenital Absence of the Cerebral Hemispheres, *Arch. Pediat.*, 1915, xxxii, 452.

OBSERVATIONS ON THE TENDENCY OF THE DIPHTHERIA BACILLUS TO LOCALIZE IN THE UPPER RESPIRATORY TRACT

THE IMPORTANCE OF THIS FACT IN ROUTINE CULTURE WORK *

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Because of past experiences in finding that the organisms of diphtheria may be present in the larynx and absent in cultures taken from the nose and throat, or positive in the nose and absent in the throat, and so on, at the suggestion of Dr. Cowie I have made a number of observations with this point in view.

Of the eight cases which I wish to report, the organisms confined themselves to one locality in five cases, which I classify as Group 1; to more than one locality in three cases, which I classify as Group 2.

GROUP 1

CASE 1.—Ione O., aged 25, with marked clinical unitonsillar diphtheria, entered the hospital Feb. 8, 1916. Diphtheria organisms were present in every culture taken from the right tonsil, absent from every culture taken from the left tonsil and pillars, the pharyngeal wall and lateral bands and from the nose. A total of thirty-three cultures, covering a period of twelve days, was taken. Antitoxin, 10,000 units, was administered intravenously, and 10,000 units intramuscularly.

On March 3, 1916, the patient returned, complaining of slight epistaxis, but a nose culture was negative.

CASE 2.—Luella S., aged 21, with marked clinical diphtheria of the lateral bands, entered the hospital Jan. 25, 1916. General cultures taken January 26 and 29 gave positive findings. Special cultures were begun February 1. The organisms were at all times present in cultures taken from the pharyngeal wall and lateral bands, but were not found in cultures taken from the tonsils and pillars or in those from the nose. A total of twenty-two cultures was taken, covering a period of twenty days. Antitoxin was administered, 10,000 units intramuscularly, 10,000 units intravenously.

CASE 3.—Ruth W., aged 21, a diphtheria carrier, entered the contagious hospital Dec. 2, 1915, having suffered with nose bleed two weeks before. General throat culture was negative; nasal culture positive. Nose and throat cultures taken simultaneously showed in each instance organisms in those taken from the nose, but not at any time in those taken from the throat. A total of thirty cultures, covering a period of twenty days, was made. The patient was discharged from the hospital after three negative cultures, the last one being taken Dec. 22, 1915.

* Submitted for publication April 27, 1916.

* From Department of Pediatrics and Contagious Diseases, University of Michigan, Ann Arbor.

March 18, 1916, she returned to the hospital, again showing positive general throat cultures. Special cultures were again instituted, and it was found that a positive culture was in each instance obtained from the pharyngeal wall and lateral bands, but cultures from the tonsillar fossae and from the nose were negative. (This patient had had adenoid and tonsil operation previous to her first entrance to the hospital.) Total cultures numbering twenty-five were taken, covering a period of fourteen days. The patient is still under observation. The Schick test is negative.

CASE 4.—Ernest D., aged 23, entered Contagious Hospital Feb. 29, 1916, showing mild clinical laryngeal diphtheria. Organisms were present in cultures taken from the larynx, but absent each time in cultures taken from the tonsils and pillars and from the pharyngeal wall and lateral bands and nose. Total cultures numbering twenty-five were taken, covering a period of sixteen days. Antitoxin was administered intravenously, to the amount of 10,000 units.

CASE 5.—Marion Y., aged 20, entered the Contagious Hospital service Jan. 5, 1916, showing laryngeal diphtheria. General culture in this case taken January 1, in the beginning of the illness, was negative. The organisms were present in cultures taken directly from the larynx until January 4. After this, cultures were taken from the tonsils and pillars, the pharyngeal wall, lateral bands and from the nose. They were in every instance negative. Total cultures numbering twenty-eight were taken, covering a period of thirty-one days. Antitoxin was administered, 10,000 units intravenously, 20,000 intramuscularly.

GROUP 2

CASE 6.—John S., aged 2, a diphtheria carrier, entered the Contagious Hospital, Dec. 9, 1915. This patient had harelip and cleft palate, enlarged tonsils and a visible mass of adenoids. A general culture, made Feb. 13, 1916, was positive and continued so until March 16, when special cultures were begun. Positive cultures were now confined to the tonsils and the visible mass of adenoids. Cultures taken from the nasal mucous membranes were negative. Total cultures numbering twenty-four and covering a period of thirty-nine days were taken. The patient is still under observation.

CASE 7.—Harry S., aged 29, a diphtheria carrier, entered the hospital Feb. 16, 1916, with facial erysipelas; the throat cultures were negative. A general culture was positive on February 27 and continued to be so until March 13, when special cultures were started. The organisms were now found present in cultures taken from the pharyngeal wall and from the nasopharynx, taken per os, but they were not found in cultures taken from both tonsils, anterior nasal passages, both right and left, and from the external auditory canal. This patient had been operated on for mastoid disease a few days before entering the Contagious Hospital. Positive cultures were obtained from the mastoid wound on three different days. The patient is still under observation. Total cultures numbering thirty-eight were taken, covering a period of thirty-eight days. It may be of interest to note that a long organism was present in this case. It has been thought that these organisms are more virulent than the short ones.

CASE 8.—Sarah S., aged 4, on Dec. 22, 1915, showed clinical nasal diphtheria, which cleared up in a few days without any antitoxin. The patient was detained because of exposure to chickenpox before entering the hospital. General routine throat culture was positive Jan. 26, 1916. Special cultures were begun February 2. They were taken with a swab, those from the tonsils and pillars, pharyngeal wall and lateral bands proving to be negative. The tonsils in this case were so large that it was impossible to reach the pharynx with a swab without touching them. A stiff platinum loop was substituted for the swab February 11. The cultures were now positive from both tonsils and negative from the pharyngeal wall and nose. Total cultures numbering thirty-three were taken, covering a period of seventy days.

CONCLUSION

1. All parts of the mucous membrane of the upper respiratory tract must be touched in making a satisfactory general culture.

2. The pharynx may be cultured and be negative for Klebs-Loeffler bacilli, but the organisms may be present in the nose or in the larynx and thus not be found except by special technic in culture work. Or as in Case 1, one tonsil may give positive cultures while all other portions of the mucous membranes may be negative. Nose bleed and hoarseness or loss of voice should attract attention to the nose or larynx.

3. Sterile cotton swabs are found to be most adaptable for getting culture material from all parts of the upper respiratory tract. Second in preference for culture taking is a platinum loop. The platinum wire must be quite heavy and stiff in order to prevent its curling and bending. It can be used only in taking cultures from tonsils, pillars, posterior pharyngeal wall and lateral bands. It cannot be used in taking nose and laryngeal cultures because of danger of trauma to the mucous membrane.

4. Several cases in this series show the necessity of having more than one or two cultures to determine that diphtheria organisms are absent from the upper respiratory tract. In this hospital at least three negative cultures are required before a patient may be discharged or before a nurse may return to the main hospital for service.

5. This interesting and peculiar tendency of the diphtheria organisms to localize in one part of the upper respiratory tract should be an important factor in deciding on surgical or medical treatment to eliminate the organisms from this part.

INFANTILE SCURVY

III. ITS INFLUENCE ON GROWTH (LENGTH AND WEIGHT)*

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In two previous papers¹ on this subject it was shown that pasteurized milk, that is, milk heated to 145 F. for thirty minutes, gradually induces infantile scurvy, unless antiscorbutic diet is given in addition. The fact that this disorder quickly yielded to the substitution of raw for pasteurized milk, or to the addition to the diet of an ounce of orange juice, or the juice of orange peel, was regarded as satisfactory evidence of the true scorbutic nature of the disturbance. The type of malnutrition which gradually develops from a diet of pasteurized milk may be termed subacute scurvy, as it takes some months to develop and, as a rule, does not manifest the pronounced symptoms characteristic of the classic case. In some instances, however, we encounter subperiosteal hemorrhages and the hemorrhagic gums typical of this disorder. That infantile scurvy is not met with more commonly, in view of the widespread use of pasteurized milk as a food for infants, may be ascribed to the fact that orange juice or other antiscorbutic food is so generally given in addition to milk. In other words, although pasteurized milk is to be recommended on account of the safety which it affords, it must be regarded as an incomplete food for infants. That the disease developing under these conditions is subacute in nature is to be attributed to the fact that the "vitamins," which are not overabundant in commercial milk, are not entirely destroyed by pasteurization, so that the infant receives day by day a small amount of these essential substances.

It will be remembered that these cases of scurvy arose in an institution where the use of orange juice was discontinued, in view of the report of the Commission on Milk Standards to the effect that milk does not suffer a destruction of enzymes or other chemical constituents in the course of pasteurization. In the first paper the nature of the hemorrhagic condition was studied, the question of involvement of the blood or of the blood vessels. In the subsequent paper the symptoms of infantile scurvy were shown to bear an intimate relationship to those

* Submitted for publication May 2, 1916.

* Presented in abstract form before the Society of Experimental Biology and Medicine, Dec. 1, 1915. (Vol. XIII. No. 3, Proceedings.)

1. Hess, A. F., and Fish, M.: *AM. JOUR. DIS. CHILD.*, December, 1914, viii, 386. Hess, A. F.: *Jour. Am. Med. Assn.*, 1915, lxx, 1003.

of other deficiency diseases, more particularly beriberi. It was pointed out that scurvy should no longer be regarded clinically as a disorder characterized merely by hemorrhages, nor from a pathologic viewpoint merely as one manifesting changes in the bones, but that signs and symptoms of involvement of the heart (enlargement of the right ventricle and tachycardia) and of the peripheral nerves are also evident, so that a broader aspect is demanded. This paper, the third in the series, which is based mainly on the same cases which formed the groundwork of the previous studies, shows how these infants reacted in their growth to alterations in diet, how they grew on a diet consisting of pasteurized milk, sugar and cereal, when they were at the same time receiving orange juice, when the orange juice was discontinued, and when this juice or the juice of the orange peel was again added to the diet. These infants offered a particularly favorable opportunity for observations of this kind because they entered the institution at an early age and remained there for one or more years, and also because they were most carefully observed, weighed daily and measured on admission and every fortnight subsequently. It was thus possible to chart their growth for more than a year and to compare their progress with that of the other infants in the institution. As far as we are aware, no study of this kind has been attempted in connection with scurvy, although it has long been known that the development of the scorbutic condition is generally accompanied by a cessation of gain in weight. Particular interest would seem to be given this investigation as the subacute type of scurvy must be considered not only the most common form of the disorder, but that which passes most often unrecognized. The opportunity presented itself to probe farther into this question of growth and to determine whether there is not likewise a stunting of the normal increment of the skeleton, an interference with the increase in length. This part of the study was judged to be of greater biologic interest than a mere observation of the effect on weight, as it is well established that infants are particularly tenacious of their impulse to grow in length, and are not readily affected in this respect by nutritional disorders, even such as reach a considerable degree of intensity. As Birk² has shown, extreme undernourishment is necessary to bring about stunting. In animals, Aron³ demonstrated that lack of nutrition led to a decrease of the fat and of the muscle in the body, but that under such conditions the skeleton continued to grow, and the ash content of the body to increase. If, therefore, this function of the body were affected, we must consider that the metabolism must be profoundly disturbed, and the deficiency of nutritional substances far reaching.

2. Birk, W.: *Berl. klin. Wehnschr.*, 1911, No. 27.

3. Aron, H.: *Biochemie des Wachstums des Menschen und der hoeheren Tiere*, Gustav Fischer, 1913, p. 58.

First, as to growth measured by weight, the various charts (Figs. 1 to 4) accompanying this article show the effect in this regard. It will be noted that although the infants continued to gain for a month or two following the discontinuance of orange juice, a decided flattening of the weight curve gradually set in, an almost constant level being maintained for weeks and months. This stationary period persisted until antiscorbutic food was once more added to the diet, when a sudden rise made itself evident. This gradual cessation of gain and sharp reaction may be stated to have been the rule, as there was but one instance in which an infant continued to gain for months in spite of the lack of antiscorbutic food. It will be seen from these charts that there was no permanent retardation of weight; in other words, the growth impulse of the body remained unimpaired and had been merely in an inactive or quiescent state. When orange juice was given once more, the rate of growth was abnormally great. There was supergrowth. Furthermore, after a period of extended observation of six months or more, it has been found that this increased rate of growth is maintained until the infant reaches a weight normal for its age. These charts seem to require but little elucidation. We may add that orange juice and orange peel juice, an infusion of one ounce of orange peel in two ounces of water, were equally efficacious in bringing about a sharp increase in weight, and that these substances apparently did not lose their potency by being boiled.

Two cases should be mentioned especially, as they represent a clinical aspect somewhat different from the others. These infants were under 6 months of age and had never received orange juice. It was possible in these instances to observe for how long a period infants will continue to gain steadily in weight on pasteurized milk before it becomes necessary to add orange juice to their diet, and to judge whether they gradually manifest a lack of gain which can be obviated by giving an antiscorbutic foodstuff. It was found that at about the seventh or eighth month a gradual but definite falling off was evident, and that this deficiency was at once corrected by adding orange juice. Figure 3 represented this condition very clearly. We note here an infant who gained about one half pound during the months of February, March, April and May, but who in June, when given boiled orange peel juice or orange juice, gained two pounds within a month. There were no other scorbutic signs or symptoms and no loss of appetite during the months of February and March, although the baby was suffering from a progressive form of scurvy. It is probable that this case and a similar one which we encountered are not solitary instances of this kind of reaction, but that many infants fail to gain at this period, the third quarter of the first year of life, for the want of this essential substance in their food, and that unconsciously this deficiency is reme-

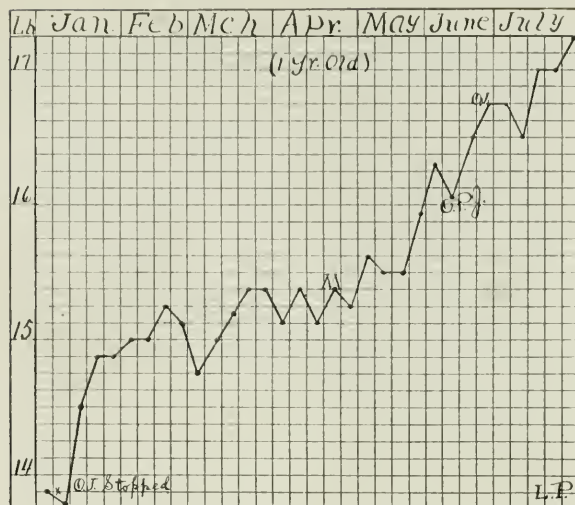


Fig. 1.—Marked gain in weight on orange peel juice and orange juice after lack of gain for three months.

In this and the following figures *O. J.* indicates orange juice; *M.* wheat middlings, and *O. P. J.* orange peel juice.

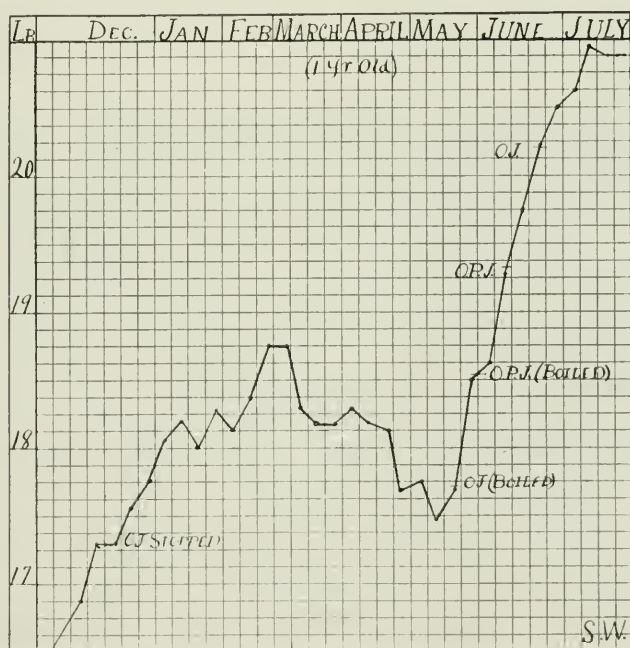


Fig. 2.—Loss of weight checked by boiled orange juice and boiled juice of orange peel.

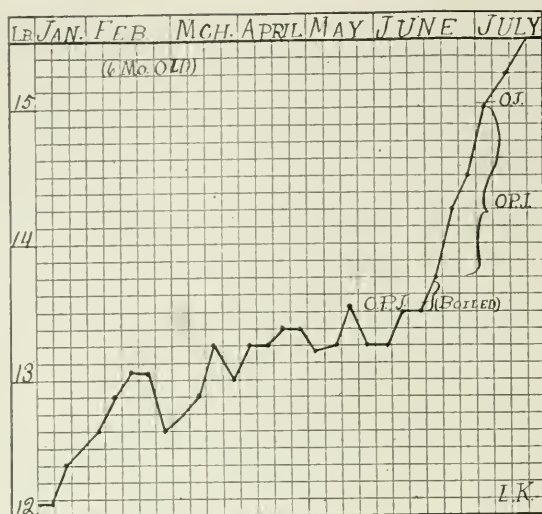


Fig. 3.—Latent scurvy in young infant who had never received orange juice. Scorbatic nature of growth disorder proved by sharp rise in weight on addition of antiscorbutic food to the dietary of pasteurized milk.

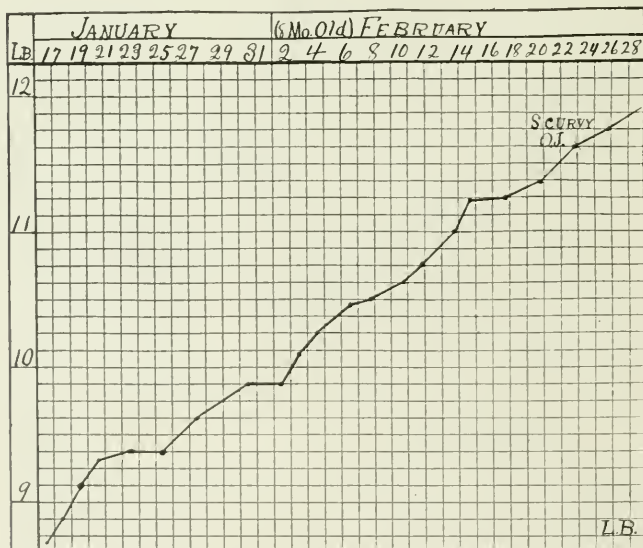


Fig. 4.—Development of scurvy in spite of normal gain in weight in a baby who had been underfed since birth.

died by adding vegetables and fruit to their dietary. We would therefore urge that antiscorbutics, for instance orange juice, be given infants at an early age. At present, the rule may be said to be to add fruit juices to the dietary at about the sixth month. This period has been chosen as the proper one, probably because scurvy rarely develops during the first half year of life. However, when we reflect that this time incidence is due to the fact that the infant is protected for the first few months of life by the supply of antiscorbutic material which it has received from the mother, and that there must be a constant negative balance of these essential substances dating from the earliest beginning of artificial feeding, it would seem as if a corrective dietary, that is to say, an antiscorbutic food, should be given as soon as practicable. There is no reason that I know of why an infant should not receive orange juice when it is a month old, and, as we have seen, there are strong arguments in favor of such a procedure.

It may be enunciated as a rule, embracing a few exceptions, that the development of the scorbutic state is generally accompanied by a failure to gain in weight. Under certain conditions, however, the weight may follow a perfectly normal course during the entire period. This observation has, from time to time, been made by others, but has received no particular consideration. It may be well therefore to cite in some detail a case of this kind, and discuss one cause of this apparently paradoxical course of events. Figure 4 illustrates this clinical paradox. The baby to whom it refers was admitted to the institution in January and was stated to be only four months of age. As a matter of fact, as we learned later, he was seven and a half months old. Toward the end of February, when he had been in the institution two months, and in spite of constant and normal gain in weight, to our surprise he manifested unmistakable signs of scurvy—peridental hemorrhage over the upper incisor teeth, which were erupting, and tenderness of the lower ends of the femora. The scorbutic nature of these signs were substantiated by their prompt subsidence on the administration of orange juice.

How is this phenomenon to be explained, normal growth during the development of scurvy, one of the classical nutritional disorders of infancy? The solution is to be found in a careful consideration of the previous diet of the baby. On investigation we found that it was born on June 5, 1915, at term, weighing six pounds, but was never nursed. For the first two weeks it received an indefinite formula prepared by the mother. From June 21 to August 19, that is, for a period of about two months, it was given a formula composed of one-fourth milk, three-fourths water, and 1.5 per cent. sugar, two ounces every three hours. In other words, it was greatly underfed for these two months. In August it weighed 8 pounds, 5 ounces. From August 19 to 27 the

formula was 30 ounces water, 12 ounces milk, and about 1 per cent sugar, four ounces being fed every three hours. This resulted in loss of weight, the baby weighing 7 pounds 15 ounces. On September 7 the formula was made one-half milk, one-half water and 1 per cent. sugar, four ounces every three hours. The underfeeding continued. On December 5 it was transferred to a hospital, where it was given a malt soup preparation for one month. It developed gastro-enteritis on January 17. As the chart shows, the child was admitted to the Hebrew Infant Asylum, weighing about $8\frac{3}{4}$ pounds at the age of $7\frac{1}{2}$ months.

If we consider the feeding of this infant, we realize that it had been almost continuously undernourished, receiving an insufficient amount of fats and carbohydrates at almost all times. At the asylum the baby was put on Schloss milk, a food containing about 4 per cent. fat and about 6 or 7 per cent. carbohydrates, seven feedings of 4 ounces in the twenty-four hours. On this it remained and, as will be seen, made steady gains until it developed scurvy toward the end of February.

This baby must be regarded as having been partially starved throughout the period following birth, with the result that on receiving a diet rich in fats and carbohydrates, foodstuffs which bring about a marked increase in weight, the reaction of the tissues was necessarily prompt and prolonged. It explains this type of case, showing that if an infant has received insufficient food, we can compel growth simply by increasing the caloric value of the dietary, notwithstanding the fact that scurvy is developing day by day. It also brings out the salient fact that more than a single cause exists leading to a repression of growth, and that therefore lack of growth must be differentiated if it is to form the basis of study. A deficiency of scurvy vitamins is one cause, lack of sufficient or adequate food is another, and, no doubt, there are still other inciting factors. Whether or not growth occurs, and to what extent, depends on the resultant stimulation which can be brought about by these various impulses. In this instance the primary growth impulse which follows a diet containing a sufficient number of calories had been held in abeyance for so many months through starvation, that when it was once more stimulated to full activity by a liberal diet, it was able to overcome the growth repression which ordinarily accompanies the development of the scorbutic condition.⁴

The foregoing illustration must make it clear that growth does not play an essential or elemental part in the constitution of infantile

4. This phenomenon probably also holds good for scurvy in the adult. A scorbutic condition may result from a lack of fresh food; but if the person has been markedly underfed, there may be a gain in weight coincident with the development of the scorbutic condition, provided liberal diet is given, including plenty of carbohydrate and fat.

scurvy. It must likewise render it evident that this study cannot be regarded as concerned with growth in general, but only with the effect of infantile scurvy on growth, as various disorders may affect this function. That such is the case is well known to clinicians and has been shown admirably in relation to animals in the recent investigations of Osborne and Mendel, of McCollum and others, which showed that growth was retarded or stimulated at will by means of diet. The results of these workers cannot, however, be considered as having any bearing on scurvy, for scurvy and growth stunting are by no means identical, either in animals or in infants. It would seem that these remarks are timely in view of a recently published study by McCollum and Davis,⁵ in which they show that the growth factor in milk is closely linked to its casein content, and preface their report by drawing an analogy to infantile scurvy, although apparently none of the animals showed any signs of a scorbutic condition.

Looking at this question from the reverse point of view, one sees clearly that factors which stimulate growth are not necessarily antiscorbutic. For example, McCollum and Davis⁶ showed that butter fat, even after it had been heated to a high degree, was able to induce growth, and Osborne and Mendel⁷ showed that this fat can be subjected to steam and not lose its growth producing power. It is nevertheless evident that butter fat in pasteurized milk does not possess sufficient antiscorbutic properties to prevent the development of scurvy, and that substances such as lysin and tryptophan, which possess marked growth promoting power, and which were present in considerable amount in our diet, were unable to make up for the dietary deficiency and bring about growth. Furthermore, cod liver oil has been found to possess growth-promoting qualities of a high degree, but there is no question that this substance, as has been shown elsewhere,¹ is incapable of preventing the development or accomplish the cure of scurvy. Before reporting additional observations as to the influence of scurvy on growth, let me add that all of the infants under consideration obtained plenty of milk, and all the older ones received cereal in addition. Particular attention was given to their obtaining a sufficient quantity, so that the factor of an insufficient diet might not enter into the question. To this end, when orange juice was discontinued, more cereal was given or the strength of the milk mixture was increased in many instances. In those cases in which there was loss of appetite, particular effort was made to have the infants take the full quantity of food, and, although the total amount consumed in many cases was not quite as much as when they were well, it nevertheless equaled that

5. McCollum, E. V., and Davis, M.: *Jour. Biol. Chem.*, November, 1915, p. 247.

6. McCollum, E. V., and Davis, M.: *Jour. Biol. Chem.*, 1913, xv, 167.

7. Osborne, T. B., and Mendel, L. F.: *Jour. Biol. Chem.*, May, 1915, p. 381.

which many infants in the institution consume and on which they continue to grow.

There is no doubt that considerable of the supergrowth which so clearly follows the giving of orange juice or its equivalent is due to an increased consumption of food. However, it would be a mistake to consider that such is entirely the case. We have reproduced two charts to illustrate this point. The first (Fig. 5) is a daily weight chart of an infant with mild scurvy, and shows the period preceding as well as

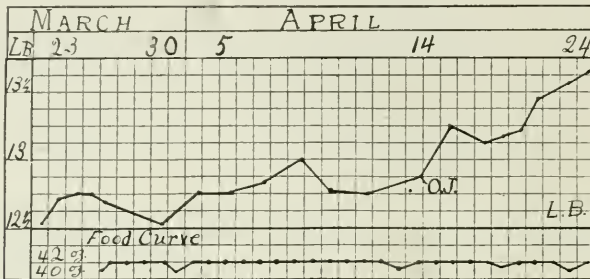


Fig. 5.—Same case as preceding. Detailed chart showing marked gain following the addition of an antiscorbutic to the diet, although amount of food remained the same.

Gain of 5 ounces in three weeks before, and 12 ounces in ten days after orange juice was given.

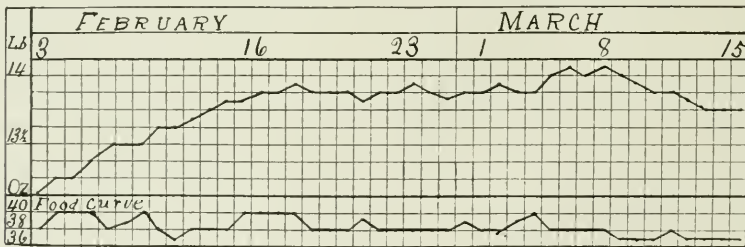


Fig. 6.—Section of a weight chart showing daily weighings during the period when gain still continued and when stationary plane was reached.

Note that the same amount of food was taken daily during the first two weeks of February, when the infant gained 12 ounces, as from the middle of February to the middle of March, when there was no gain whatever.

This baby had latent scurvy and responded promptly to orange juice.

that following the giving of orange juice, together with the food intake (Schloss milk). Although it will be seen that there was no change in the amount of milk taken before and after giving orange juice, there was a marked difference in the gain; the infant increased only 5 ounces in weight during the three weeks in which it did not obtain orange juice, and 12 ounces in ten days following its addition to the diet.

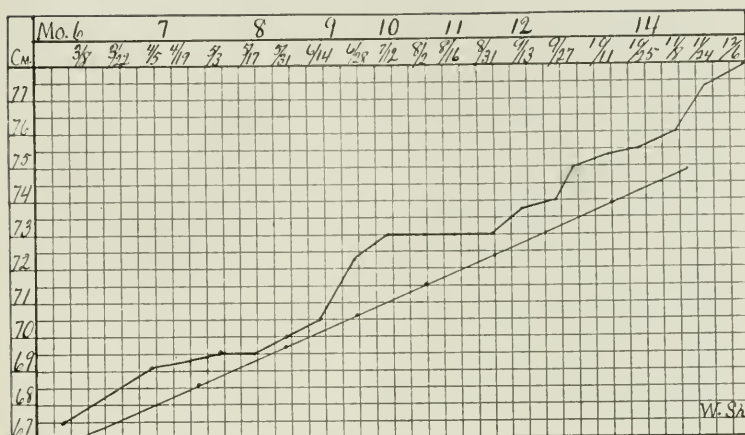


Fig. 7.—Growth in length from the sixth to the fifteenth month of healthy baby receiving orange juice. The lower line represents the average growth.

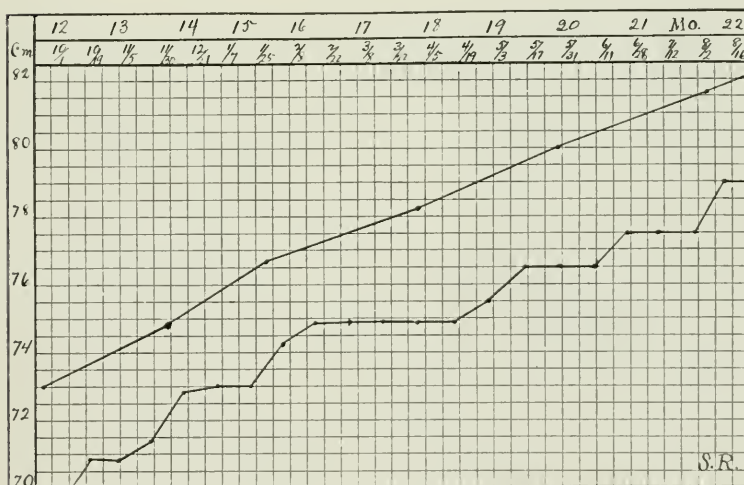


Fig. 8.—Growth in length from the twelfth to the twenty-second month of a very small, healthy baby receiving orange juice.

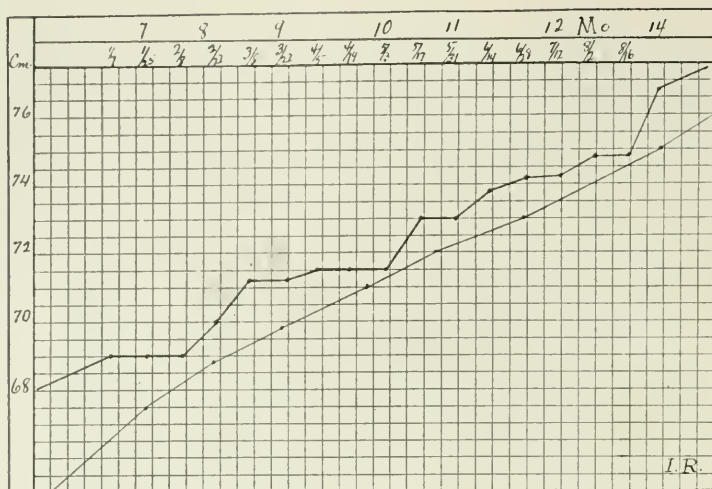


Fig. 9.—Growth in length from the seventh to the fourteenth month of a large healthy baby receiving orange juice.

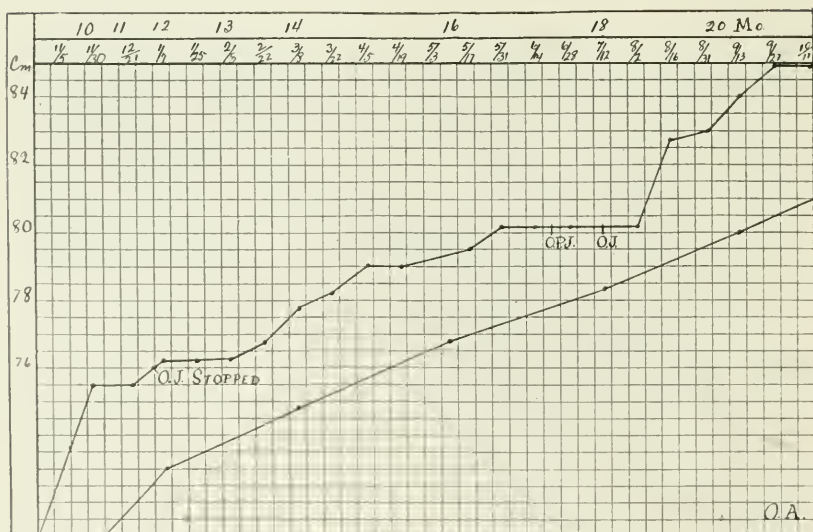


Fig. 10.—Growth in length for a period of five months during which no orange juice was given, compared with subsequent months when it was again added to the diet.



Fig. 11.—Length chart of young infant (illustrated in Fig. 3) who had never received orange juice. Marked reaction in growth in length when an anti-scorbutic was added to the diet.

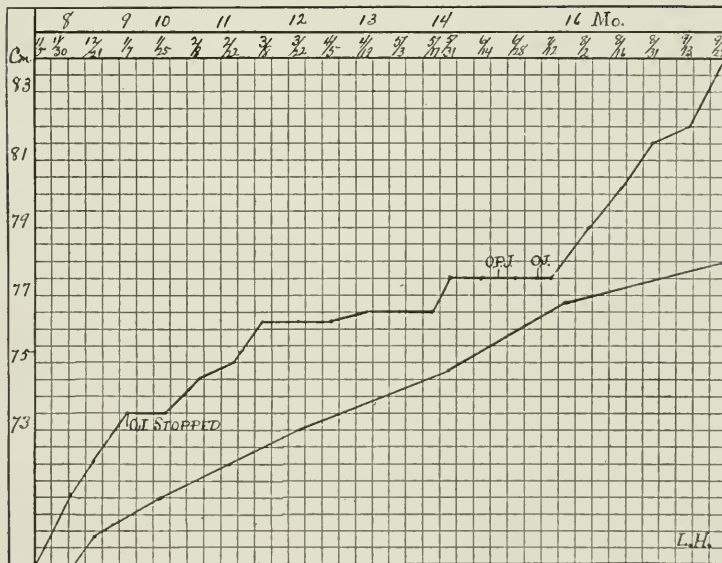


Fig. 12.—Showing retardation of growth in length during the period when no orange juice was given, and supergrowth when it was given once more.

Figure 6 shows another aspect of this question. It demonstrates that the period of gradual growth stagnation, on which infants fed entirely on pasteurized milk enter as the result of not receiving an antiscorbutic, is not due to a lack of food. Here we note the gradual inception of this stationary phase, from a period of gain, in spite of the fact that the intake of food remained undiminished. It is evident, therefore, that neither the lack of gain in the course of the development of infantile scurvy, nor the increase of weight coincident with its cure, can be considered to be dependent on the caloric value of the dietary.

As has been mentioned above, a study of the growth in length was also carried out, the measurements being taken fortnightly for over a year. In order to furnish a basis for comparison, the growth of ten normal infants who received orange juice, but otherwise the same diet, was followed at the same time. The charts which we reproduce clearly bring out the distinction between the two groups of cases. Figures 7, 8 and 9 illustrate the growth of the normal infants, and constitute a standard by which to judge the others. They portray a consistent, although slightly irregular, growth month by month. Quite in contrast to these curves are those depicted in Figures 10, 11 and 12, representing three infants who did not receive orange juice from January to May.

Figure 11, which represents growth in length complements Figure 3, representing growth in weight, and illustrates the case of a young baby who had never received orange juice, and developed a latent or rudimentary form of scurvy when about eight months of age. These three cases, when contrasted with the normals, leave no question that the scorbutic condition has a decided effect on growth in length as well as in weight, and that this impulse remains unimpaired in both respects and capable of quick response when the essential foodstuff is furnished.

CONCLUSIONS

Although pasteurized milk is to be recommended on account of the security which it affords against infection, we should realize that it is an incomplete food. Unless an antiscorbutic, such as orange juice, the juice of orange peel, or potato water is added, infants will develop scurvy on this diet. This form of scurvy takes some months to develop and may be termed subacute. It must be considered not only the most common form of this disorder, but the one which passes most often unrecognized. In order to guard against it, infants fed exclusively on a diet of pasteurized milk should be given antiscorbutics far earlier than is at present the custom, even as early as at the end of the first month of life.

In the course of the development of infantile scurvy, growth, both in weight and in length, is markedly affected. Under these conditions,

weight ceases to increase, and a stationary plane is maintained for weeks or for months. There is a quick response, however, on the administration of orange juice or its equivalent, indeed supergrowth is thereupon frequently manifested. If, however, an infant has been underfed, an increase in weight may continue throughout the development of the scorbutic condition. Cessation of growth, as well as marked increase in growth, may manifest themselves, although the caloric value of the food remains unchanged, depending merely on the withholding or the addition of essential foodstuffs to the diet.

Measurements showed that growth in length is also retarded during the protracted development of infantile scurvy. This is of greater biologic interest, as simple malnutrition usually does not affect this function in the infant. In this particular, supergrowth also follows the addition of the essential foodstuff, showing that the growth impulse has remained uninjured and has been merely held in abeyance.

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PROGRESS IN PEDIATRICS

RESUME ON INFECTIOUS DISEASES *

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The chief general advances made in contagious diseases in the past few years are the wider use of the so-called aseptic technic with the handling of cases, based on the notions of Grancher, and a tendency to attempt active immunization as a means of either preventing these diseases or forestalling their manifestation in a severe form.

HOSPITAL CARE

The newer view of the hospital care of patients with contagious diseases admits as possible and desirable their maintenance in all cases in the same building or even in the same ward with general nursing. Its success seems to depend almost entirely on the conscientiousness with which doctors and nurses carry out the few simple technical precautions, which are in fact almost identical with those observed in the surgical operating room.

The article by Richardson¹ gives a brief résumé of work previously done, especially in English hospitals, with description of hospital and technic used. Three per cent. cross infections is reported as the average. Similar hospitals in this country are in operation at the University of Michigan,² in Evanston,³ and in Chicago.⁴

One of the others under construction is to be at Iowa City. An attempt was made to introduce this system in the new children clinic of Vienna,⁵ and over 10 per cent. of cross infections were reported, the high figure being due no doubt to the well-known inferiority of continental nurses. Connell⁶ describes the Monsall Hospital, Manchester, where this same method is being used. There have been as yet no official reports from the newer hospitals, although at Ann Arbor the percentage of cross infections during the

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* From the Department of Pediatrics, University of Michigan, Ann Arbor.

1. Richardson, D. L.: Jour. Am. Med. Assn., 1913, lxi, 1882.

2. Tr. Clin. Soc. Univ. Mich., 1913-1914, v, 90.

3. Sturm, M. J.: Mod. Hosp., iii, 3.

4. Durand Hospital.

5. Von Pirquet, C.: Ztschr. f. Kinderh., 1912, v, 213.

6. Connell, W. T.: Canad. Med. Assn. Jour., May, 1912, xli, 594.

first year was about 2. Phillips⁷ urges the early isolation of all patients with mild or severe cases. In a series of 900 patients taken care of by the aseptic method there were but two cross infections.

Disinfection after contagious diseases has been discontinued in New York for four years. Chapin⁸ shows that, in the instances of diphtheria and scarlet fever, recurrences have not increased in number, being 1.53 per cent. after 1908 and 1.48 per cent. before in scarlet fever, and 1.75 per cent. after 1908 and 1.71 per cent. before in diphtheria. Bedding disinfection is also dispensed with.

CHICKENPOX

Greeley⁹ describes what he believes to be the etiologic agent of chickenpox, smallpox, and vaccinia. This is a sporothrix which corresponds to the *cytorrhyses variolae* (Councilman). It passes through the Berkefeld filter No. 5 and does not grow on artificial media. Mycelial growth is said to be obtainable.

Kling¹⁰ is the first to have successfully inoculated against varicella. He took the contents of the vesicle of a case at the height of the disease and injected it intradermally in fifty-eight patients, avoiding when possible the drawing of blood. On the eighth day one, usually more, small, red papules appeared. These suggested the lesions seen in cowpox. After a day or so a small, raised, red zone developed about these papules, from which vesicles appeared, which dried up in three or four days, the scab of which did not disappear for two or three weeks. The material from this vesicle could be used for inoculating other nonimmune individuals. Occasional rise of temperature was reported, but rarely illness or general rash. It is interesting to note that in several patients previously inoculated with cowpox vaccine a positive result was obtained, further evidence of the nonidentity of the two viruses. Of the patients inoculated, none developed chickenpox, although they had been exposed. Handrick¹¹ attempted to repeat this work, using the percutaneous method, with negative results. Tieche¹² describes a simple method of differentiating between chickenpox and variola, which depends on the fact that the intradermal inoculation of material from the smallpox lesion will give a positive reaction in the immunized individual, that is to say, vaccinated, whereas no reaction is obtained with the content of the varicella vesicle. By heating the suspected material for five minutes at

7. Phillips, C. H.: Brit. Med. Jour., 1912, No. 2694, p. 357.

8. Chapin: Medical Officer, 1913, ix, 218.

9. Greeley, H.: Med. Rec., New York, 1914, lxxxvi, 204.

10. Kling, C. A.: Berl. klin. Wchnschr., 1913, I, 2083.

11. Handrick, E.: Monatschr. f. Kinderh., 1914, xiii, 242.

12. Tieche: Cor.-Bl. f. Schweiz. Aerzte, 1913, xliii, 735, 779; Ibid., 1914, xliv, 1121.

80 F. an earlier reaction was obtained. These tests were done by the experimenter on himself.

Besides these articles several clinical reports may be quoted. For example, Heim¹³ tells of a family in which the mother had herpes zoster. Some weeks after this both children had measles with zoster-like arrangement of the lesions. Lereboullet and Moricand¹⁴ report a case of varicella contracted at birth from the mother, the disease appearing fourteen days after birth. Lentz¹⁵ tells of an instance of indirect transmission in which the child apparently infected its two sisters and mother with the disease and later itself became infected from these patients, thus carrying the disease without infecting itself. Three cases of acute appendicitis occurring during the course of measles are reported by Perier.¹⁶ Storrie¹⁷ has encountered two cases of hemorrhagic and gangrenous varicella. Krause¹⁸ reports cases of varicella in adults, which he believes to be very rare. The diagnosis was verified by the method of Tieche. Lilienthal¹⁹ reports six cases of varicella in adults, diagnosed as syphilis.

EPIDEMIC PAROTITIS

Little work of importance is reported on this subject. Feiling²⁰ studied the blood and spinal fluid in forty cases. He noted a slight absolute and relative increase of the white corpuscles and an early increase of the lymphocytes. In one case orchitis and leukopenia, with relative increase of polymorphonuclears, were found. The spinal fluid was studied when meningeal symptoms, such as vomiting, amblyopia, drowsiness and loss of patellar reflexes, were present. The fluid was found to be colorless and slightly turbid, with 2,500 white blood cells per cubic millimeter, of which 96 per cent. were mononuclears. Barach²¹ studied the blood and found a leukopenia of 5,000 to 600 cells at the outset of the disease and over 48,000 at the height. With the subsiding of the parotid tumor the leukocytes tend to increase. He says that the lymphocytes are increased in number while the polymorphonuclears become fewer. The eosinophils disappear, to return later in greater number than normal. Friedjung²² reports a case of recurrence of mumps in a 15-month-old baby after an interval of slightly over four months.

13. Heim, P.: *Berl. klin. Wchnschr.*, 1912, xlix, 2349.

14. Lereboullet, P., and Moricand, J.: *Arch. de méd. d. enfants*, 1914, xvii, 288.

15. Lentz, O.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 1148.

16. Perier, E.: *Ann. de med. et chir. inf.*, 1914, xviii, 7.

17. Storrie, H. C.: *Brit. Jour. Child. Dis.*, 1914, xi, 62.

18. Krause, P.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 881.

19. Lilienthal, L.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 1247.

20. Feiling, A.: *Lancet*, London, 1913, No. 4689, p. 71.

21. Barach, J. H.: *Arch. Int. Med.*, 1914, xii, 791.

22. Friedjung, J. K.: *Jahrb. f. Kinderh.*, 1913, lxxvii, 197.

The investigation of mumps in England by H. M. Gordon²³ shows that the highest mortality occurs in patients under 5 years and especially under 1 year. Gordon²⁴ also gives the pathologic findings in four fatal cases of mumps, the patients being from 2 to 4 years of age, death coming early, with a clinical picture of meningoencephalitis. The lumbar fluid showed increased pressure, with lymphocytosis. The salivary glands were clinically negative, but on histologic examination they showed a marked interstitial inflammation in the perivascular and excretory duct region. On Berkefeld filtration the material obtained from some of these cases seemed capable of producing meningitis and parotitis in monkeys. Acker²⁵ reports two cases complicated with meningitis. Dracinski and Mehlmann²⁶ have seen three cases of pancreatitis complicating mumps. The onset was with fever and headache and the patient presented severe symptoms of collapse, epigastric pain, vomiting, Cheyne-Stokes breathing, delirium, loss of patellar reflexes and acetonuria. Two cases of oöphoritis are reported by Brooks.²⁷ In one of these an abscess formed requiring incision. In the other both breasts atrophied. Conception did not take place in either case within the five years the patients were under observation.

MEASLES

Epidemiology and Prophylaxis.—Rohmer²⁸ analyzed a hospital epidemic and concluded that in the average case measles is infectious for at least seven days, that is, during the period of invasion and exanthem, but not during desquamation. The patients were all confined to their beds and the disease consequently carried from one to the other by the nurses or by utensils. Raffie²⁹ shows quite conclusively that school closure when measles appears is the most effectual method of controlling the disease. Thus, of 4,470 children, 2,180 were susceptible. There were 618 cases of measles before school closed and only 140 within fourteen days after closing, while but seventy-five new infections developed during the third week. Cohn³⁰ is of the same opinion, urging that all who have not had the disease be excluded at least fourteen days. Craster,³¹ in an interesting study of measles among immigrant children, showed that most cases appeared in June. The largest complication average a case mortality occurred in infant. The

23. Gordon, H. M.: Jour. Am. Med. Assn., 1914, lxiii, 414.

24. Gordon, H. M.: Lancet, London, 1913, clxxxv, 275.

25. Acker, G. N.: AM. JOUR. DIS. CHILD., 1914, vi, 399.

26. Dracinski, N., and Mehlmann, J.: Deutsch. med. Wchnschr., 1914, xl, 1566.

27. Brooks, H.: Jour. Am. Med. Assn., 1913, lx, 359.

28. Rohmer, P.: Jahrb. f. Kinderh., 1912, lxxv, 78.

29. Raffie, A. B.: Lancet, London, 1912, clxxxi, 294.

30. Cohn, M.: Ztschr. f. Schulgsndhtpf., 1914, pp. 654, 723.

31. Craster, C. V.: AM. JOUR. DIS. CHILD., 1914, vi, 122.

seasonal prevalence of complication was greatest in winter (December), with the case mortality highest in January. Otitis was the most frequent complication.

Corney³² describes an epidemic of measles in an island of the South Sea, which was like the classic outbreak in the Faroe Islands. Of the nearly 2,000 inhabitants one fourth died, the death rate between the years up to 5 and between 20 and 25 years being greatest. Of the fatal sequelae bronchopneumonia, phthisis and ileocolitis were prominent. Mery and Malhene³³ emphasized the fact that this disease has the greatest mortality in asylums and in foundlings' homes. For example, the total mortality in the institutions of France studied was 11 per cent. of the inmates. If the deaths from measles had been excluded, the mortality would have been 5 per cent. Kilbourne³⁴ reports 600 cases of measles occurring among adults in the Columbus barracks. The mortality was 5 per cent. This figure should be compared with the report of Crum,³⁵ who shows the mortality in patients over 20 years to be 0.3 per cent.; the mortality in patients from 1 to 4 years is 1 per cent., while in those under 1 year of age it is 3.5 per cent. The lowest mortality is found between the years of 5 and 9, when 0.2 per cent. is given. The lowest mortality thus occurs in patients infected between the ages of 5 and 19 years. These figures should guide us in quarantine and prophylaxis.

Pathology.—The loss of allergy occurring during measles is shown in several new ways by recent investigations. Thus Koch³⁶ shows strikingly the relationship that the various stages of measles bear to the loss of the power to react against infection. In the days immediately before and after the appearance of the exanthem, most purulent and secreting processes temporarily cease, for example, the fistula of the cold abscess, the reaction of meningitis, and the cavity of empyema. During the period of the rash there is a failure to react to tuberculin and vaccine, serum rashes and psoriasis. In the week following the exanthem there is the well-known increased tendency to purulent processes and their spread, together with the liability to thrombosis, embolism, necrosis and gangrene. Neumark³⁷ reports a case of a 3-year-old child, who developed the rash of measles four days after being vaccinated. The first typical vesiculation was not noted until eleven days after scarification, a delay of about four or five days. The reaction was normal from that time on.

32. Corney, B. G.: Brit. Jour. Child. Dis., 1913, x, 252.

33. Mery, H., and Malhene: Bull. Soc. de pédiat. de Paris, 1913, xv, 1.

34. Kilbourne, E. D.: Mil. Surgeon, 1912, xxxi, 294.

35. Crum, F. S.: Am. Pub. Health, 1914, iv, 289.

36. Koch, H.: Ztschr. f. Kinderh., 1914, xi, 267.

Tunncliffe³⁸ has found a distinct diminution of phagocytic activity of the leukocytes for streptococci, staphylococci and tubercle bacilli, during the period of the leukopenia, with the return to normal of the blood the phagocytic index also tended to increase. In cases of monkeys inoculated with the blood of measles patients a similar phenomenon is observed. Moltschanow³⁹ shows that the loss of tuberculin sensitiveness is independent of the fever and complications, but is in close association with the rash. Lucas and Prizer⁴⁰ and Nicolle and Conseil⁴¹ verify the work of Hektoen and of Anderson and Goldberger by injecting the blood of measles patients intracerebrally and intraperitoneally.

The incubation period was found to be six days, the Koplik spots appearing on the average of four days later. The virus was transmitted from one ape to the second and from the second to the third. They assume that the virus is in the blood within twenty-four hours after the buccal spots appear and thirty-six hours after the beginning of the skin eruption. A leukopenia is found in the preeruptive stage. The latter observers also find the virus in the blood nine days after inoculation. C. von Pirquet⁴² applies his theory of incubation to this disease. He assumes that the infecting micro-organisms enter the body and during incubation there is developed the so-called *ergin*, which has the character of an antibody. This takes part in the digestion of the invading micro-organisms, with the result that there is formed a toxic product, or apotoxin, which in turn produces the fever, enanthem, and exanthem. The quick death of the virus explains the definite and rapid ending of the disease. He believes also that the process of agglutination plays a part in the formation of the rash. Just why the apotoxin should appear first, and possibly in the greatest quantity, in the tissues of the head is not clearly explained. It seems necessary, however, that the tissues must be saturated with a certain amount of this substance and that, therefore, the regions with the richest blood supply receive the greatest amount of the antibody and so show the rash first.

Remembering the work of Pfeiffer on the toxicity of the urine in anaphylaxis, Aron and Sommerfeld⁴³ examined the urine in a series of cases of measles, intravenously injecting from 1 to 2 c.c. into a

38. Tunncliffe, R.: *Am. Jour. Infect. Dis.*, 1912, xi, 474.

39. Moltschanow, B.: *Russk. Vrach.*, 1911, No. 43; abstr., *Jahrb. f. Kinderh.*, 1912, lxxi, 619.

40. Lucas and Prizer: *Jour. Med. Research*, April, 1912, xxvi, 181.

41. Nicolle, C., and Conseil, E.: *Paris Letter, Jour. Am. Med. Assn.*, 1912, lviii, 289.

42. Von Pirquet, C.: *Ztschr. f. Kinderh.*, 1913, vi, 1.

43. Aron, H., and Sommerfeld, P.: *Deutsch. med. Wchnschr.*, 1912, xxxviii, 1733.

guinea-pig. While from 2 to 4 c.c. normal urine were well borne, 2 c.c. were stated to have been sufficient to produce quick death, with the symptoms of anaphylaxis. The substance is thermostable and dialyzable. There seems to be no relationship with the period of exanthem. The duration of excretion of the poison varies in different individuals. These investigators had negative results with the urine of patients with typhoid fever, pertussis, scarlet fever and diphtheria. The urine derived from a patient with serum exanthem and fourth disease gave positive results. Mautner⁴⁴ comes to a different conclusion, in that while the urine of measles patients was toxic, the same property was found in specimens voided by those infected with diphtheria, peritonitis, scarlet fever, valvular heart disease and arthritis.

Koch⁴⁵ describes a prodromal rash occurring in one fourth of his cases. This consisted in brownish-red, macular, illly defined spots, fleeting in character. They appeared chiefly on the face at the time or immediately after Koplik spots are seen. A further aid in the early diagnosis of measles comes from Grumann.⁴⁶ On both tonsils he found punctate and linear whitish swellings of about 3 mm. in length in the neighborhood of the lacunar depressions; these might also be seen on the more prominent follicular eminences. They seemed to appear either coincidentally with the Koplik spots or they might be present alone when the Koplik spots were absent, tending to precede the eruption by one or two days. He suggests that they may be superficial infiltrations or necroses. Lucas,⁴⁷ studying the blood in measles, found that the change in the differential picture took place about a week before the appearance of the characteristic symptoms. This consisted in the replacement of the normal relative mononuclears by a polynuclear increase. Some disintegrated cells were found, which, while not specific, when taken with the above transformation were of importance in epidemics, enabling earlier isolation without waiting for the appearance of the Koplik spots. Lutz⁴⁸ gives the necropsy findings in twenty-two cases of measles in which thrombus formation was encountered. Of these, six cases involved chiefly the pulmonary artery, while in two cases portal veins were partly obstructed.

Epidemiology and Mortality.—Feibelmann⁴⁹ reports two cases in which measles occurred a second time in the same individual. In one

44. Mautner, H. L.: Deutsch. med. Wchnschr., 1912, xxxviii, 1815.

45. Koch, H.: Ztschr. f. Kinderh., 1913, ix, 1.

46. Grumann, M.: München. med. Wchnschr., 1914, lx, 132.

47. Lucas, W. P.: AM. JOUR. DIS. CHILD., 1914, vii, 149.

48. Lutz: Berl. klin. Wchnschr., 1913, l, 1566.

49. Feibelmann: Arch. f. Kinderh., 1911, lvii, 50.

of these it was impossible to determine whether the disease was to be recorded as a recurrence or a second infection. Koplik spots were found in each instance. Only five such cases are reported in the literature. On the other hand, Friedjung⁵⁰ reports three persons who, though definitely exposed, did not contract the disease, the patients now being 17, 19 and 19 years of age, respectively. It is possible that this is one of the rare cases of natural immunity. The striking influence of good hygienic surroundings on mortality is shown in the report of Maier.⁵¹ Since the contagious patients have been moved into new quarters, the mortality from measles has been halved.

Complications and Sequelae.—Weill and Gardere⁵² found an infectious erythema occurring in eight severe cases, of which four of the patients died. This erythema appeared at symmetrical points, distributed on the extremities, the trunk and abdomen not being involved except occasionally where the rash tended to become general. This was associated with ulceration in the mouth, in the cheek and in the pharynx, where Hutinel believes that secondary invaders found portals of entry. The mucous membrane lesions, however, were not necessarily present. There may be a succession of eruptions which are independent of the severity of the mucous membrane lesions or the severity of the disease. Clinical symptoms of the secondary infection may precede the rash. Griscom⁵³ found double choked disk occurring in a patient in the third week of the disease. Complete recovery took place. Morgenstern and Gruber⁵⁴ found multiple infarcts of the skin in a poorly nourished, rickety infant 1 year old. Multiple necrotic areas on the outer and lower side of the thigh below the gluteal fold were the chief lesions. Death occurred on the fifth day following the appearance of the rash. Delcourt⁵⁵ found two cases of subcutaneous emphysema as a complication of bronchopneumonia. This he interprets as being due to perforation of adherent lung. Ligabue⁵⁶ reports a case of subphrenic abscess following measles. Fischl⁵⁷ saw a case in which a hemorrhagic diathesis appeared following the disease with resulting enormous subcutaneous hemorrhages. Pertussis was also present. Galop⁵⁸ adds to the cases of gangrene of the limbs. Bronchopneumonia and enterocolitis were also present.

50. Friedjung, J. V.: Wien. med. Wchnschr., 1914, p. 939.

51. Maier, L.: München. med. Wchnschr., 1913, lx, 636.

52. Weill, E., and Gardere, C.: Rev. de méd., 1913, xxxiii, 545.

53. Griscom, M.: Ann. Ophth., 1912, xxi, 42.

54. Morgenstern and Gruber: Ztschr. f. Kinderh., 1914, xii, 100.

55. Delcourt: La Patholog. Infantile, 1914, xi, No. 1.

56. Ligabue, P.: Policlinico, Rome, xxi, No. 7.

57. Fischl: München. med. Wchnschr., 1912, lix, 621.

58. Galop, M.: Arch. de méd. d. enfants, 1914, xvii, 49.

Just before the appearance of the complications the popliteal pulse could not be felt, while the femoral pulse was still present.

Treatment.—Temporary interest was aroused by a rather extravagant statement of Milne,⁵⁹ who said that if as soon as possible after the outbreak of the rash pure eucalyptus oil were rubbed over the body of the patient twice a day and the tonsils swabbed every two hours with a solution of 10 per cent. phenol in oil for the first twenty-four hours, isolation became unnecessary and complications and secondary infections were prevented and disinfection rendered needless. Even the eating utensils were not sterilized. Elgart⁶⁰ repeated this and found that while it did not do all that its author predicted, it did seem to produce a diminished mortality. It is not uninteresting to find that he did not use phenol, finding that 50 per cent. lime water was as efficient and that he did not rub the body with the eucalyptus. Connolly⁶¹ also believes that he has had help from this method, in that in comparative groups the mortality was but 5 per cent. among severe cases, whereas it was 11 per cent. in a similar group untreated. Marfan⁶² shows that salvarsan given to a child as treatment for syphilis did not protect it against measles. This treatment has been more used in cases of scarlet fever, where further reference will be made to it.

GERMAN MEASLES

Outside of studies in hematology little of importance has been reported. Schwaer⁶³ finds a slight increase in the white cells with the mononuclears relatively greater in number. A leukopenia is not characteristic, as stated by many. The eosinophils, which disappear in measles at the height of the disease, are said to be constantly present in this disease. Hamburger⁶⁴ denies the report that he saw the eosinophils increase at the height of measles eruption. Saito⁶⁵ was fortunate enough to see an epidemic of 105 cases, including seventeen adults and six infants. The incubation period seemed to vary from fifteen days to twenty-three days. In only thirteen cases was the temperature over 100 F. The rash was of the characteristic papular type with anemic margins. Glandular enlargement was constant. The white blood count varied between 6,000 and 12,000 cells. Saito, in contrast with Schwaer, found the polynuclear cells relatively increased. Eosinophilia at the period of the fading rash was common, one case

59. Milne, R.: *Lancet*, London, 1911, p. 1070.

60. Elgart, J.: *Med. Klin.*, 1913, ix, 1251.

61. Connolly, D. L.: *Practitioner*, London, 1912, lxxxix, 664.

62. Marfan, A. B.: *Paris Letter*, *Jour. Am. Med. Assn.*, 1912, lviii, 1387.

63. Schwaer: *München. med. Wchnschr.*, 1913, ix, 1203.

64. Hamburger, F.: *München. med. Wchnschr.*, 1913, ix, 2120.

65. Saito, H.: *Ztschr. f. Kinderh.*, 1914, x, 54.

of 42 per cent. being noted. No loss of susceptibility to tuberculin was made out as in cases of measles.

WHOOPING COUGH

Statistics and Epidemiology.—Emphasis has again, in the past few years, been laid on the high mortality from whooping cough. Morse⁶⁶ shows that while it causes the smallest number of deaths, 11.4 per 100,000, of the four important contagious diseases, still the percentage of mortality is very high and more attention should be paid to prophylaxis and isolation. Rucker⁶⁷ comments on the recent public health reports which state that 10,000 children a year are sacrificed to this disease. Pisek⁶⁸ finds the mortality in New York City to be over 10 per cent. of reported cases. According to his figures many of these died of tuberculosis. He urges special hospitals for the detention of such patients. An objection to the institutional care of such patients on the basis of the influence of proximity and the resulting suggestion is raised by Galisch.⁶⁹

Experimental Work and Diagnosis.—Inaba⁷⁰ was able microscopically as well as culturally to demonstrate the Bordet-Gengou organism in 90 per cent. of his cases. A not uninteresting part of this report is the statement that the influenza bacillus differs from the organism of whooping cough in its cultural characteristics. The author finds that the whooping cough bacillus has more resistance and does not seem to have the same tendency to pleomorphism that the influenza bacillus has. He recognizes defibrinated goat's blood agar as the best medium for the cultivation of the bacteria. Manicatide⁷¹ finds an organism which he denominates bacillus Z as the etiologic agent of whooping cough. This organism resembles the organism of influenza. He finds that the serum of both goats and sheep can be used for treatment and prophylaxis. The work surely needs further confirmation.

Diagnosis of the cough from similar clinical stages is determined by several authors by means of the reaction of complement deviation. Delcourt⁷² finds it of special service. Friedlander and Wagner⁷³ use the fresh antigen, this being a seventy-two hour culture on ascitic agar. Fresh serum is also used. By this means they believe that they are able to diagnose the presence of the disease in its earlier stages, in

66. Morse, J. L.: Jour. Am. Med. Assn., 1913, ix, 1677.

67. Rucker: Jour. Am. Med. Assn., 1912, lix, 1882.

68. Pisek: New York Med. Jour., 1914, xcix, 970.

69. Galisch, A.: Med. Klin., 1912, viii, 488.

70. Inaba, I.: Ztschr. f. Kinderh., 1912, iv, 252.

71. Manicatide, M.: Ztschr. f. Kinderh., 1913, vii, 226.

72. Delcourt, A.: La Patholog. Infantile, 1912, ix, No. 1.

73. Friedlander, A., and Wagner, E. A.: Jour. Am. Med. Assn., 1914, lxii, 1008.

contradistinction to Bacher and Metchnikoff,⁷⁴ Bordet,⁷⁵ and Netter and Weill,⁷⁶ who were able, by employing the usual technic, to find a positive reaction only at the height of the disease or in convalescence. Thirty examinations on eighteen cases were positive in the paroxysmal stage; in three cases two positive results were found even in the catarrhal stage. Neurath⁷⁷ attempted to produce an intracutaneous specific allergic reaction with the endotoxin of the Bordet-Gengou bacillus. No reliable results were obtained. Both control and patient, with the exception of a few infants, were positive.

An interesting contribution to the pathologic anatomy of whooping cough was made by Mallory and Horner.⁷⁸ They found that the cilia of the epithelial cells lining the trachea, bronchi, and possibly the nose were, in the specimens examined, covered with a thick layer of minute bacilli, and believe that the location of the organism is apparently characteristic of the disease and that the action seems to be partly mechanical, producing inhibition of the ciliary movements and of the cellular secretions. The blood changes have again been studied by Schneider,⁷⁹ and they are in the main confirmatory of previous workers. His results may be summarized briefly by stating that there is a leukocytosis up to 80,000, the average being 27,000. The mononuclears are relatively increased during the first four weeks, 86 per cent. being the highest and 60 per cent. the average. No prognostic conclusions can be drawn from the blood picture.

Clinic and Complement.—That the notion regarding pertussis, supported by Czerny, who overemphasized the neurotic element, a stand which he has recently disavowed, should find some adherents is not surprising. Dobelli⁸⁰ took up this view and was vigorously combated by Feer.⁸¹ Feer admits the psychic element, but believes that it is possible that Czerny was deceived by pertussis-like cough of tuberculosis or that occasionally following pneumonia. The association of pertussis and spasmophilia has been the subject of several communications. Wernstedt⁸² tells of an epidemic in which the patients showed increased irritability of the nerves, but no evidence of the presence of specific organisms. Erlanger⁸³ denies a necessary association between the two conditions.

74. Bacher and Metchnikoff: *Centralbl. f. Bakteriöl., Orig.*, 1912, lxi, 218.

75. Bordet: *Centralbl. f. Bakteriöl., Orig.*, 1912, lxvi, 236.

76. Netter and Weill: *Compt. rend. Soc. de biol.*, 1913, lxxiv, 236.

77. Neurath, R.: *Med. Klin.*, Berlin, 1914, x, 1619.

78. Mallory, F. B., and Horner, A. C.: *Jour. Med. Research*, 1912, xxvii, 115.

79. Schneider: *München. med. Wchnschr.*, 1914, lxi, 303.

80. Dobelli, E.: *Cor.-Bl. f. schweiz. Aerzte*, 1912, Nos. 4 and 23.

81. Feer, E.: *Cor.-Bl. f. schweiz. Aerzte*, 1912, No. 6.

82. Wernstedt, W.: *Hygiea*, Stockholm, September, 1912; *abstr.*, *München. med. Wchnschr.*, 1912, lix, 605.

83. Erlanger, B.: *Monatschr. f. Kinderh.*, xii, No. 8.

A number of interesting complications and sequelae are again reported. Roedelius⁸⁴ has seen a case of optic atrophy, the seventh on record. He believes this to be due to neural infections as well as to the mechanical influences. Sylvester⁸⁵ reports eight patients with cerebral complications, of whom seven died. In two, micro-organisms were demonstrated in the spinal fluid. Weigert⁸⁶ saw a meningocele develop in an infant after three weeks of coughing. Later, as the fontanels grew smaller, the tumor disappeared. No permanent injury of the brain was demonstrable. Two months following a severe pertussis polydipsia developed in an 8-year-old patient of von Starch.⁸⁷ The diabetes mellitus which was diagnosed was of slight severity.

Vaccine Treatment.—The vaccine treatment of whooping cough has been quite frequently reported. Ladd⁸⁸ reports eight patients, of whom three were infants. From 40,000,000 to 50,000,000 bacteria were given. The average duration of the disease was eight weeks. The author draws no definite conclusions as to the beneficial results produced, but feels that the severity of the paroxysms was diminished. Zahorsky⁸⁹ reports favorably of his experience. He attributes to the vaccine a certain immunizing power. Nicolle and Connor⁹⁰ treated 104 patients and saw fifty-seven cured, thirty-eight improved, while twenty-five were uninfluenced. Bamberger⁹¹ had six cases in which he gave 21,000,000 bacteria every day for from five to fifteen days. This author believes that both the symptoms and severity of the disease were abated and that fewer complications were noted. According to Wilson,⁹² whenever a systemic reaction was produced by the vaccine an improvement followed. In his twenty-three cases he used a total of 60,000,000 to 80,000,000 bacteria and felt that a distinct benefit was produced. Sill⁹³ has a series in which the patients' ages range from six months to three years. In the patients earliest seen the improvement was the most marked. Individual doses of from 2,000,000 to 6,000,000 were given, but improvement was frequently not seen until three injections had been given. In one case he gave a total of 220,000,000 bacteria, at the rate of 40,000,000 every second day. Two exposed patients had weekly injections of 20,000,000 bacteria and did not contract the disease. Scott⁹⁴ also was satisfied with the vaccine

84. Roedelius, E.: Arch. f. Kinderh., 1913, lxii, 161.

85. Sylvester, P. H.: Boston Med. and Surg. Jour., 1914, clxx, 406.

86. Weigert, R.: Monatschr. f. Kinderh., 1914, xiii, 139.

87. Von Starch, W.: München. med. Wchnschr., 1912, lix, 1317.

88. Ladd, M.: Arch. Pediat., 1912, xxix, 581.

89. Zahorsky, J.: Interstate Med. Jour., 1912, xix, 844.

90. Nicolle and Connor: Compt. rend. Acad. d. sc., 1913, No. 24, p. 1849.

91. Bamberger, A.: AM. JOUR. DIS. CHILD., 1913, v, 33.

92. Wilson, S. M.: New York Med. Jour., 1913, xcvi, 823.

93. Sill, E. M.: AM. JOUR. DIS. CHILD., 1913, v, 379.

94. Scott, G. D.: New York Med. Jour., xcvi, 176.

treatment, in that a distinct ameliorating influence on the symptoms was found. Luttinger⁹⁵ used the vaccine in severe cases in which medicine was of no avail, and in ten of these cases was able to diminish the severity of the paroxysms as well as to shorten the duration of the disease. He believes that he was successful in immunizing against the disease one exposed patient by the use of 50,000,000 bacteria. He prefers the subcutaneous injection. His highest total dose was 150,000,000. One of the most interesting contributions to our knowledge of the use of vaccines comes from Hess,⁹⁶ who describes his experience in an orphan asylum of 357 inmates, the patients varying in age from a few days to 6 years. The vaccine was used by him chiefly for prophylactic purposes, although it was also used in treatment. Of 240 patients who were vaccinated with from 100,000,000 to 2,000,000,000 bacteria, twenty, or 8.3 per cent., developed the disease. Of eighty who were definitely exposed, or, to put it in its most unfavorable light, of 130 who were not vaccinated, fifty-nine, or 22 per cent., developed the disease. If the degree of exposure in the two groups of cases was at all comparable, the results are surely most striking. This observer has less favorable statements to make as to the therapeutic efficiency of the vaccine, in that he did not even observe a distinctly beneficial influence on the symptoms. Hartshorn and Moeller⁹⁷ found that a certain number of patients improve with commercial vaccine, others did not. They urge the continuation of its use only when a quick and distinct benefit is found. Graham⁹⁸ sums up his experiences by stating that about three fourths of the patients are symptomatically benefited. He also ascribes a certain prophylactic value to the vaccine.

It seems probable that any conclusions as to the efficiency of the vaccine treatment of pertussis must be guarded. Knowing the numerous remedies suggested in the past, enthusiastically acclaimed and as quickly dropped from our armamentarium, one wonders whether the vaccine will have the same fate. The reports seem to show, with few exceptions, an influence on the symptoms. Whether this benefit is in the eyes of the observer or is a real one only the future can tell. The further use of the vaccine seems, however, to be definitely indicated. Patients should be treated early and vigorously, but this treatment should be discontinued if beneficial effects are not obtained. While vaccine therapy is still in the experimental stage, still more is this true with regard to the use of the vaccine as a prophylactic. No

95. Luttinger, P.: *Med. Rec.*, New York, 1913, lxxxiv, 1125.

96. Hess, A. F.: *Jour. Am. Med. Assn.*, 1914, lxxiii, 1007.

97. Hartshorn, W. M., and Moeller, H. N.: *Arch. Pediat.*, 1914, xxxi, 587.

98. Graham: *Arch. Pediat.*, 1914, xxxi, 578.

harmful results have been reported, however, and there seems no reason why further investigations should not be carried out.

Miscellaneous Treatment.—Popper⁹⁹ urges suggestive treatment with the faradic treatment in the later stages of the disease. Ochsenius¹⁰⁰ favors local treatment of the pharynx with 2 per cent. silver nitrate. This also has a psychic effect. Rusca¹⁰¹ reports an interesting case in which a little patient with pertussis was operated on for a complicating appendicitis. The pain produced by coughing made the child exert its will to control the paroxysms. This emphasizes the psychic element of the disease.

DIPHTHERIA

Statistics and Epidemiology.—The great interest shown in diphtheria in recent years is due undoubtedly to the fact that although we have an effective means of diagnosis and treatment, still the morbidity rate and mortality has not tended to show so great a diminution as might be expected. Abel,¹⁰² speaking of conditions in Germany from 1892 to 1898, shows that the total number of deaths from diphtheria in one year is greater than those from scarlet fever. The city mortality is higher than that of the country. He urges more intensive and more systematic cultures in order to control this condition. Braun¹⁰³ also emphasizes this fact in regard to the city of Berlin. Von Drigalski¹⁰⁴ shows that by systematic culturing and isolation it was possible to rid a population of nearly 200,000 of much of its diphtheria. In this connection reference should be made to the excellent treatise by von Behring¹⁰⁵ on the subject of the control of contagious diseases. Seligman and Schloss¹⁰⁶ describe in detail their carefully controlled attempts to weed out diphtheria in several schools and institutions. Throughout the report they emphasize the necessity of systematic culturing, as well as the desirability of routine cultures, before patients are admitted. The significance of snuffles in infants is also recognized, although they fail to give sufficient mention to this same symptom in older children. Details relating their experiences with treatment, etc., are given.

Teague¹⁰⁷ reports some experiments done to show how far droplet infection plays a part in the spread of the disease. He found that in

99. Popper, E.: *Med. Klin.*, 1913, No. 26.

100. Ochsenius: *Therap. d. Gegenw.*, 1913, liv, 502.

101. Rusca, F.: *Cor.-Bl. f. schweiz. Aerzte*, 1914, No. 19.

102. Abel, R.: *Centralbl. f. Bakteriöl.*, 1912, lxiv, 229.

103. Braun, W.: *Deutsch. med. Wehnschr.*, 1912, xxxix, 255.

104. Von Drigalski: *Berl. klin. Wehnschr.*, 1912, xlix, 1792.

105. Von Behring: *Einführung in die Lehre von der Bekämpfung der Infektionskrankheiten*.

106. Seligman, E., and Schloss, E.: *Ztschr. f. Kinderh.*, 1912, iv, 451.

107. Teague, O.: *Jour. Infect. Dis.*, 1913, xii, 398.

talking or coughing only small numbers of droplets are emitted and these but a few inches from the mouth, thus forcing the conclusion that contact infection direct or indirect, is, as in other contagious diseases, the chief method of propagation. That one attack of diphtheria does not confer a lasting immunity is shown by Montefusco,¹⁰⁸ who saw a patient with three clinical attacks in eight months. Reiche¹⁰⁹ writes of his experience in a recent severe diphtheria epidemic in Hamburg, in which he encountered 344 patients who had previously had diphtheria. Of these, 119 had never received antitoxin.

Carriers and Contacts.—Von Hoff¹¹⁰ concludes that in a large number of cases diphtheria bacilli will persist up to five months after the disappearance of the clinical symptoms, even though the cultures are negative. After this they tend to diminish. Brückner¹¹¹ and others bring out a most interesting fact, namely, that at certain times of the year at Dresden it seems that the percentage of bacillus carriers undergoes an enormous but not to be explained increase, up to 48 per cent. of examined cases. These cultures are found in a large number of children who are not clinically ill. It is not stated, however, whether this increase is connected with the increase of the number of clinical cases of diphtheria and whether these patients are not really contacts. This brings up, of course, the well-known difficulty of determining the significance of the culture morphologically positive. Van Biemsdyk¹¹² found among thirty-three children, nineteen of whom had just had diphtheria, organisms resembling Klebs-Loeffler bacillus in twenty-four instances. Of these, but two were virulent. In a region free from diphtheria for ten years, in 50 per cent. of children examined the same organisms were found. His criteria of virulence were the formation of acid and agglutination in a dilution of at least 1 to 500. Riebold¹¹³ saw an epidemic produced in a children's colony by a carrier. Delyannis¹¹⁴ also emphasizes the importance of isolation and treatment of carriers. In three villages endemic diphtheria was not controlled until the carriers had been recognized. Arms and Whitney¹¹⁵ also emphasize the rôle of contact in the spread of diphtheria.

Pathologic Anatomy and Physiology.—Abramow¹¹⁶ studied the hypophysis in experimental diphtheria and believes that there is an early hyperstimulation and hypersecretion with resulting exhaustion.

108. Montefusco, A.: Gazz. d. osp., March 16, 1913, xxxiv, No. 32.

109. Reiche, F.: Med. Klin., 1913, ix, 1668.

110. Von Hoff, G.: Monatschr. f. Kinderh., 1914, xiii, 133.

111. Brückner: Abstr., München. med. Wchnschr., 1913, ix, 554, 609.

112. Van Biemsdyk, J. M.: Nederl. Tijdschr. v. Geneesk., 1914, p. 1066.

113. Riebold, G.: München. med. Wchnschr., 1914, lxi, 923.

114. Delyannis, K.: Wien. klin. Wchnschr., 1913, xxvi, 1389.

115. Arms and Whitney: Am. Jour. Pub. Health, 1912, No. 10, 799.

116. Abramow, S.: Virchows Arch. f. path. Anat., 1914, ccxiv, 408.

It is interesting to note, however, that the first changes appear in the adrenal. The author, however, does not definitely state that there is an interrelation between these two glands. Kreutsfeldt and Koch¹¹⁷ also find the pars intermedia of the hypophysis markedly affected, there being in guinea-pigs a diminution in size with granular cystic degeneration. Wildebrand¹¹⁸ examined the hypophysis in fatal cases of diphtheria in children and finds again distinct degenerative changes in the pars intermedia. He emphasizes the therapeutic value of pituitrin in these severe cases of diphtheria. Moltschanoff¹¹⁹ again emphasizes the marked change in the adrenal glands and sees in this pathology the justification for the great potency of epinephrin in cardiac collapse.

Involvement of the heart in diphtheria is commented on by Rohmer.¹²⁰ In two cases, although heart block was demonstrated by the electrocardiogram at autopsy, the His bundle was found to be relatively unaffected. Tanaka,¹²¹ however, finds a uniform diffuse degeneration of the auriculoventricular bundle, although in one case of severe arrhythmia this muscle filament showed no change. Several other communications have appeared on this subject. Wilson¹²² in his résumé refers to the chief of these.

While it has been commonly assumed that the vasomotor center is greatly affected and is believed to be the cause of the circulatory collapse in diphtheria intoxication, Porter and Pratt¹²³ in their animal experiments have been unable to find evidence to bear out this statement. The earlier views have been probably due to faulty interpretation of experiments. This is one other fact which tends to indicate that suprarenal failure plays an almost sole part in this condition. The finer mechanism of this is shown by McCallum¹²⁴ in the isolated heart of an animal, with an artificial circulation containing diphtheria toxin. He shows that if there is sufficient pressure in the coronary artery, the heart will still beat for hours. Leede¹²⁵ examined the blood in fatal cases during an epidemic of unusual severity. Out of 256 cases he found the streptococcus in 205, the pneumococcus in twenty-three, the Klebs-Loeffler bacillus in nine, and the latter in conjunction with streptococcus in four. Liedke and Volckel,¹²⁶ however, in seven

117. Kreutsfeldt, G., and Koch, R.: *Virchows Arch. f. path. Anat.*, 1913, cxxiii, 123.

118. Willebrand: *Zentralbl. f. d. ges. inn. Med. u. d. Grenzgeb.*, 1912, iii, 132.

119. Moltschanoff, W.: *Jahrb. f. Kinderh.*, 1912, Supplement 200.

120. Rohmer, P.: *Jahrb. f. Kinderh.*, 1912, lxxvi, p. 391.

121. Tanaka: *Virchows Arch. f. path. Anat.*, 1912, ccvii, 113.

122. Wilson, F. N.: *AM. JOUR. DIS. CHILD.*, 1915, x, 376.

123. Porter, W. T., and Pratt, J. H.: *Am. Jour. Physiol.*, 1914, xxxiii, 431.

124. McCallum, W. G.: *Am. Jour. Med. Sc.*, 1914, cxlvii, 37.

125. Leede, W. H.: *Ztschr. f. klin. Med.*, 1913, lxxvii, 297.

126. Liedke and Volckel: *Deutsch. med. Wchnschr.*, 1914, xl, 594.

fatal cases, found diphtheria bacilli in the heart, lungs, spleen, kidneys and in the bone marrow. Reye,¹²⁷ in sixty-seven cases, found bacteria in the lungs fifty-six times. Of these, the diphtheria bacillus was in pure culture but six times; twenty-seven times it was associated with streptococci and in twenty-three cases with other micro-organisms.

Bacteriology.—Unending attempts are being made to simplify the interpretations of the laboratory findings in diphtheria and to bring them into harmony with the clinic. The fact that the mere morphology gives no positive information and the fact that not only in the culture but also in the throat the organisms of diphtheria tend to undergo involution, though apparently retaining the power to again become virulent, make the problem almost hopelessly difficult. Thiele and Embleton¹²⁸ report that they have been able to transmute a characteristic Hoffman diphtheroid into a virulent organism with the typical morphology of the diphtheria bacillus, capable of producing pathologic changes in a guinea-pig. The significance of this is at once apparent. If verified, it would indicate that the involution types of organisms found in the respiratory tract of the patient so many months after the disappearance of clinical symptoms are still capable of producing infection. The opposite has been accomplished by Römer.¹²⁹ He transforms the virulent into an avirulent modification by passage through guinea-pigs. Meunier still adheres to the commonly accepted views that the polar body organisms and the barred and solid types are the only ones to be feared. Baerthlein¹³¹ found that in progressive cultures the diphtheria bacilli lost their virulence, and with this is associated a change in the form and appearance of the colony produced. Kolmer,¹³² from a large series of cultures, concludes that only the granular type, using the classification of Westbrooke, are virulent. The barred types are of doubtful significance, while the small forms may be excluded, unless small polar granules are found, when they are to be regarded as positive. Kolmer,¹³³ using the complement fixation reaction as a basis for classifying the diphtheria-like bacilli, shows that all of them are related and that the true Hoffmann bacillus is probably an example of mutation.

There is no relation between the occurrence or degree of complement fixation and the antitoxin strength of the immune serums. This again brings up the fact, commonly overlooked, that not only is there

127. Reye, E.: München. med. Wchnschr., Oct. 29, 1912, lix, 2383.

128. Thiele and Embleton: Ztschr. f. Immunitätsforsch. u. exper. Therap., 1913, xix, 643, 666.

129. Römer, P. H.: Berl. klin. Wchnschr., 1914, li, 503.

131. Baerthlein, K.: Berl. klin. Wchnschr., 1913, l, No. 22.

132. Kolmer, J. A.: Jour. Infect. Dis., 1912, xi, 56.

133. Kolmer, J. A.: Jour. Infect. Dis., 1912, xi, 44.

an antitoxic, but also an antibacterial, immunity developed. Menard,¹³⁴ cultivating diphtheria bacilli on serum in contact with antitoxin, found them unaffected; they seemed, however, to lose their power of producing toxin. Lavari¹³⁵ in this connection has been able to find by means of the complement fixation test that there is an antibacterial amboceptor to be found in antitoxin. No conclusions are drawn as to its significance. Townsend¹³⁶ reports the finding of virulent pseudodiphtheria bacilli in the urinary tract. Kolmer¹³⁷ in forty cases made 100 cultures from the penis, and finds diphtheroid bacilli which, however, he states to be avirulent.

Cultural Methods.—Conradi and Troch¹³⁸ describe a new medium for elective culture of diphtheria bacilli. This consists in ordinary beef serum in which is incorporated a small percentage of sodium tellurate and of calcium malate. The diphtheria bacilli are first grown on ordinary Loeffler's serum for three hours and are then transferred to plates of the new mixture. The diphtheria bacilli colonies are supposed to reduce the tellurate, a black colony resulting. Other micro-organisms are stated not to do this. Calcium malate is supposed, moreover, to retard the growth of these other organisms. Several investigators have used this plan and their reports are far from enthusiastic. Hanau¹³⁹ sees no proportionate advantage over the older method. Klunker¹⁴⁰ is of the same opinion. Schurmann and Hajos,¹⁴¹ however, used the Conradi-Troch plates and omitted the simple serum altogether. They found a larger number of positive cultures as well as a simplification of the picking out of colonies. Wagner¹⁴² found no more positive results, but found it easier to locate the organisms. Markl and Pollak¹⁴³ speak well of this new medium.

Another improvement is suggested by von Drigalski and Bierast.¹⁴⁴ They add 3 per cent. sterile ox bile to Loeffler's glucose bouillon serum. Voelckel,¹⁴⁵ Schulz,¹⁴⁶ and Grundman¹⁴⁷ are not favorably impressed with their experiences. Conradi¹⁴⁸ has an ingenious technic for sepa-

134. Menard, P.: Presse méd., 1913, xxi, 636.

135. Lavari: Ann. d. Ist. Maragliano p. la cura d. tuberc., 1913, vii, No. 2.

136. Townsend, W. W.: Jour. Am. Med. Assn., 1913, lxi, 1605.

137. Kolmer, J. A.: Arch. Pediat., 1912, xxix, 94.

138. Conradi and Troch: München. med. Wchnschr., 1912, lix, 1652.

139. Hanau: Centrabl. f. Bakteriöl., 1913, lxxii, 245.

140. Klunker: München. med. Wchnschr., 1913, lx, 1025.

141. Schurmann, W., and Hajos, E.: Deutsch. med. Wchnschr., 1913, xxxix, 786.

142. Wagner, G.: München. med. Wchnschr., 1913, lx, 457.

143. Markl and Pollak: Wien. klin. Wchnschr., 1913, xxvi, 1617.

144. Von Drigalski, W., and Bierast: Deutsch. med. Wchnschr., 1913, xxxix, 1327.

145. Voelckel, E.: München. med. Wchnschr., 1913, lx, 883.

146. Schulz, F. C. R.: Deutsch. med. Wchnschr., 1913, xxxix, 2195.

147. Grundmann: Berl. klin. Wchnschr., 1913, l, 2287.

148. Conradi, P.: München. med. Wchnschr., 1913, lx, 1073.

rating the diphtheria bacilli from other micro-organisms, based on the fact that if a mixed culture be shaken up in a test tube containing salt solution and oil, the diphtheria bacilli will be taken up by the oil, whereas the rest of the organisms go into the salt solution. Cotton swabs surrounded by filter paper and moistened with ligroin are dipped into the oil later, the oil passing through the paper into the cotton and the bacteria remaining on the filter paper. Af Heurlin¹⁴⁹ attempts to differentiate by cultural methods the true and the false diphtheria bacilli. This is based on the capacity which the true diphtheria bacilli have of developing without oxygen. Consequently, in deep stabs into alkaline phenolphthalein glucose agar, the true bacilli will be toward the bottom. On blood glucose phenolphthalein agar it is found that pseudodiphtheria bacilli do not produce hemolysis.

Immunology.—Interesting steps in advance are found in the introduction of the intradermal application of diphtheria toxin for clinical purposes by Schick and a like clinical application by von Behring of a suggestion made first by Theobald Smith, namely, that mixtures of toxin and antitoxin be used to actively immunize against diphtheria. The first full communication of Schick¹⁵⁰ has to do with the application of the so-called Römer test and the first observations were done with the blood serum of a diphtheria patient to determine the toxin content.

In another communication he¹⁵¹ finds that local hypersensitization does not result, even though the tests be frequently repeated. He also used this method¹⁵² as a means of determining the amount of diphtheria antitoxin necessary to neutralize circulating toxin and found that by giving as little as 500 units per kilogram of body weight (250 units per pound) in 91 per cent. of all cases the toxin reaction could be prevented. In other words, this amount of antitoxin was sufficient to neutralize not only the circulating toxin, but also that amount in addition which was introduced for the test. No retroactive power of the serum could be made out—another confirmation of the importance of early treatment. Prophylactic injections were given only to those patients who had a positive toxin test. He¹⁵³ suggests that if the intracutaneous tests are negative, there are sufficient protective bodies in the patient's serum, and he also concludes that there is an immunity in these cases. As to whether the diphtheria bacillus might not gain a hold in the mucous membrane in spite of this immunity is not discussed. The strength of

149. Af Heurlin, M.: München. med. Wehnschr., 1914, lxi, 703.

150. Schick, B., and Michiels, J.: Ztschr. f. Kinderh., 1912, v, 255.

151. Schick, B.: Centralbl. f. Bakteriöl., 1912, lxvi, 121.

152. Schick, B.: Wien. klin. Wehnschr., 1914, xxvii, 1966.

153. Schick, B.: München. med. Wehnschr., 1913, lx, 2608.

the toxin suggested for this test is such that 0.1 c.c. is equivalent to $\frac{1}{50}$ of the lethal dose for a guinea-pig which weighs about 250 gm.

Park, Zingher and Serota¹⁵⁴ have tried out this reaction in 700 cases of scarlet fever. Fifty-seven per cent. (400 cases) gave negative reaction and developed no diphtheria, although the patients did become carriers. Using this reaction, they also found that the intravenous administration of serum was more effective than the subcutaneous or intramuscular. Kleinschmidt¹⁵⁵ found that of eighteen infants, sixteen showed no antitoxin in the blood. The two patients in whom antitoxin was found were in an institution where they may have been exposed. Of sixteen infants who were bacillus carriers, antitoxin was found in the blood of ten, as much as 2.5 units per cubic centimeter being determined. Otto¹⁵⁶ found that the percentage of antitoxin in adults is greater in those who are frequently exposed to diphtheria, as in a hospital. Carriers and excretors of the bacilli also showed a high content. An acute infection gives only a moderate immunity, whereas a chronic infection is necessary for this purpose. Larval infections, without symptoms, are especially potent. Schütz¹⁵⁷ also in a series of cases finds that the Schick test gives a definite clue as to the susceptibility of the patients. Hahn¹⁵⁸ also, using the method of Römer, shows that attendants in diphtheria wards and others frequently exposed have the highest antitoxin content of the blood. Kassowitz and Gröer¹⁵⁹ show that the immunity of the new-born, which exists in 80 to 90 per cent. of all cases, depends on the antitoxin derived from the mother's blood. Beyer¹⁶⁰ found that antitoxin was found in the blood of every patient who had been injected, from one-half to four-fifths of the total quantity being present. On the fifth and the sixth days from one-fifth to three-tenths were still present. In from two to three weeks only from five- to six-hundredths could be demonstrated. In certain instances a larger amount was found than would be theoretically expected. Harriehausen and Wirth¹⁶¹ found toxin in the blood of patients with diphtheria, using the Römer method. Less than 0.1 c.c. of serum was sufficient to produce necrosis and, indeed, in one fatal case 0.04 c.c. caused a very severe necrosis in twelve hours. In ten cases of postdiphtheritic paralysis toxin was found five times.

Theobald Smith in 1903 found that a mixture of diphtheria toxin and antitoxin, in which the former was in slight excess, caused a pro-

154. Park, Zingher, and Serota: *Arch. Pediat.*, 1914, xxxi, 481.

155. Kleinschmidt, H.: *Jahrb. f. Kinderh.*, 1913, lxxviii, 442.

156. Otto, R.: *Deutsch. med. Wchnschr.*, 1914, xl, 542.

157. Schütz: *München. med. Wchnschr.*, 1913, lx, 2608.

158. Hahn: *Deutsch. med. Wchnschr.*, 1912, xxxviii, 1366.

159. Kassowitz and Gröer: *Abstr.*, *Jahrb. f. Kinderh.*, 1913, lxxviii, 609.

160. Beyer, W.: *Deutsch. med. Wchnschr.*, 1912, xxxviii, 2353.

161. Harriehausen and Wirth: *Ztschr. f. Kinderh.*, 1913, vii, 132.

duction of a large amount of antitoxin in the blood without producing serious symptoms and suggested then that this method might be used to advantage in children. Von Behring¹⁶² was the first to apply this on a large scale and sent out mixtures for use, determining that the observations should be made with the greatest exactness possible by means of regular examination of the content of the blood of the children immunized. His program is a model of thoroughness. He states in his first communication that the presence of 0.1 of a unit per cubic centimeter of blood was sufficient to protect individuals during an epidemic; with the injection of 100 units into a child the antitoxin disappears in 20 days after reaching 0.025 per c.c. If a homologous serum is used, the passive immunization endures a considerably longer time. He notes that the assumption of the permanent binding of toxin and antitoxin in vitro is a false one and also that the proportion of toxin and antitoxin which will produce symptoms varies with the different species. The human animal is not sensitive at birth, but becomes so after it has been exposed to infections, bacillus carriers, for example, being especially sensitive and producing antitoxin easily. He made a further observation, which requires confirmation, however, that those treated with this new mixture, which will hereafter be referred to as T. A., did not harbor the diphtheria bacilli even though exposed. The experimental work, which is best seen in the original, as, for example, in the article by Viereck,¹⁶³ contains many interesting observations. He shows among other things that the adult is 100 times more sensitive, per kilogram of body weight, than is an infant. Zangemeister¹⁶⁴ also finds this lack of susceptibility in the new-born and in those not infected. The method of administration is described by Schreiber.¹⁶⁵ About 0.1 c.c. of the mixtures, of which there are several, is used at intervals of from three to five days and is given as often as three times. Its effect is noted in from twenty-three to twenty-five days. The lowest serum content produced per cubic centimeter was 0.75, the highest 1, although by repeated injections (four to seven), as much as from 10 to 75 units per cubic centimeter was obtained. The author maintains that there must be from 0.04 to 0.1 per cubic centimeter for effective protection. He found four failures in twenty-one cases.

Kleinschmidt and Viereck¹⁶⁶ prefer the intracutaneous rather than the subcutaneous method of administration. Not only is there heightened immunizing power, but there is an added advantage in that the susceptibility of the individual is indicated by the reaction following the

162. Von Behring: *Deutsch. med. Wchnschr.*, 1913, xxxix, 873.

163. Viereck: *Deutsch. med. Wchnschr.*, 1913, xxxix, 978.

164. Zangemeister, W.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 977.

165. Schreiber, E.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 928.

166. Kleinschmidt and Viereck: *Deutsch. med. Wchnschr.*, 1913, xxxix, 1977.

injection. For example, there may be no more than simple redness produced in some cases, while in others a more general reaction, with fever, malaise, headache and swelling of the lymph glands follows. If the second injection produces a local reaction with distinct redness and swelling, they expect to find about 0.5 units of antitoxin produced per cubic centimeter of blood. Kissling¹⁶⁷ immunized 310 children by this method and of the 111 children who received two prophylactic injections, none contracted diphtheria. Of the 119 who received but one, eight developed the disease. Von Behring and Hagemann¹⁶⁸ also used the intracutaneous method, using 0.1 c.c. of total solution, but they were not of the opinion that the degree of local reaction was an indication of the amount of antitoxin formed. Bauer¹⁶⁹ was unable to free ten carriers of their bacilli by this method. Park, Zingher and Serota¹⁷⁰ used the Schick test to determine whether the active immunization was indicated and found that two thirds did not require it. They determined that the active immunity might not develop until late and when produced lasted from one to two years. Kohn and Sommers¹⁷¹ used this method in five epidemics, 633 cases in all being immunized. They also used the intracutaneous method. Of these patients only two developed the disease and that in a mild form.

Schrieber¹⁷² reports a total of 700 patients treated, of whom but twelve developed diphtheria. Blacher¹⁷³ has analyzed the various types of gallop rhythm. His most important conclusion is that an increase in peripheral resistance is one of the causes, so that it is not necessarily an index of the myocardial change. He assumes that the heart in diphtheria is very sensitive to all stimuli—nervous, mechanical, etc.

Diagnosis and Clinical Findings.—That there may be some difficulty in the diagnosis of diphtheria is shown in the communication of Charlier,¹⁷⁴ who states that phlegmonous angina and malignant diphtheria are almost indistinguishable and if the possibility of the latter disease is not borne in mind and no cultures taken, unsuitable treatment may be instituted. The association of Vincent's angina and diphtheria, or the presence of diphtheria bacilli in cases which are clinically Vincent's angina, is described by Reiche.¹⁷⁵ The author, however, does not discuss the question of serum therapy. Weill¹⁷⁶ summarizes the vari-

167. Kissling: *Deutsch. med. Wchnschr.*, 1913, xxxix, 2500.

168. Von Behring and Hagemann: *Berl. klin. Wchnschr.*, 1914, li, 917.

169. Bauer, J.: *Deutsch. med. Wchnschr.*, 1914, xl, 582.

170. Park, Zingher and Serota: *Jour. Am. Med. Assn.*, 1914, lxiii, 859.

171. Kohn and Sommers: *Deutsch. med. Wchnschr.*, 1914, xl, 13.

172. Schreiber: *Therap. d. Gegenw.*, 1914, lv, 98.

173. Blacher, W.: *Jahrb. f. Kinderh.*, 1914, lxxix.

174. Charlier, G.: *Hygiea, Stockholm*, lxxv, No. 6; abstr., *Jour. Am. Med. Assn.*, 1913, lxi, 1084.

175. Reiche, F.: *Med. Klin.*, 1914, x, 1381.

176. Weill, E.: *Patholog. Infantile*, 1913, x, 101.

ous faucial manifestations of diphtheria and emphasizes especially the perforating, ulcerating, anginal form, which is of a very severe character and which has a tendency to form ulcers in the soft palate, in the gums and other portions of the buccal mucous membrane. Various secondary invaders are found on culture. Lind¹⁷⁷ emphasizes the fact that pharyngeal diphtheria may run a mild course without membrane formation, the diagnosis not being made unless cultures are taken. He fails to state whether or not nasal diphtheria, so commonly associated with this type of infection, was present.

The need of emphasizing the significance and frequency of nasal diphtheria is shown in numerous articles. Moss¹⁷⁸ calls attention to it from the point of view that it is a neglected source of infection in the public schools. Conradi¹⁷⁹ describes the prevalence of nasal diphtheria in infants with nutritional disturbances and shows that serum therapy is without effect. Von Bokay¹⁸⁰ reports two cases of diphtheria of the gums in infants in whom the initial infection was in the nasal tract.

Forbes and Newsholme¹⁸¹ discuss the possible association of membranous rhinitis and diphtheria. For therapy they prefer an autogenous vaccine composed of streptococci and Klebs-Loeffler bacilli. They did not use serum. David¹⁸² assumes that he has seen a case of acute primary diphtheritic pneumonia. A secondary rise in temperature following the crisis led to death. At necropsy tracheal diphtheria was made out and the diphtheria bacilli cultivated in almost pure culture from the lungs. Tylecote¹⁸³ reports a case of diphtheria of the stomach with fatal outcome. Cargin¹⁸⁴ reports a case of membranous enteritis, diphtheritic membranes being passed during the ten days of the illness. Pollak¹⁸⁵ observed a case of diphtheritic sepsis following an infection which resulted from the piercing of the ears in an infant. Kleinschmidt¹⁸⁶ is able to corroborate the statement of Bingel that the intracutaneous injection of toxin produces a very great response in the formation of antitoxin. In the case of anal diphtheria Blühdorn¹⁸⁷ reports epidemics in which the cases were of unusual severity, so that from 20,000 to 30,000 units of antitoxin were insufficient to prevent postdiphtheritic palsies.

177. Lind, S. C.: *Jour. Am. Med. Assn.*, 1913, ix, 1412.

178. Moss, E.: *New Orleans Med. and Surg. Jour.*, 1913, lxxv, 703.

179. Conradi, E.: *München. med. Wehnschr.*, 1913, ix, 512.

180. Von Bokay, Z.: *Ztschr. f. Kinderh.*, 1914, xi, 191.

181. Forbes and Newsholme: *Lancet*, London, 1912, No. 4614, p. 292.

182. David, O.: *München. med. Wehnschr.*, 1913, ix, 2431.

183. Tylecote, F. E.: *Brit. Jour. Child. Dis.*, 1913, x, 211.

184. Cargin, H. M.: *Lancet*, London, 1913, No. 175, p. 23.

185. Pollak, R.: *Wien. klin. Wehnschr.*, xxvi, 1306.

186. Kleinschmidt: *München. med. Wehnschr.*, 1913, ix, 1477.

187. Blühdorn, K.: *München. med. Wehnschr.*, 1912, lix, 1266.

Diphtheria bacilli in the urine are found by numerous observers. Koch¹⁸⁸ took 111 samples from twenty-six patients and found characteristic virulent micro-organisms four times in the urine of two patients. They were found, however, only in the early stages in severe cases in which the patients died with symptoms of cardiovascular failure. Conradi and Bierast¹⁸⁹ found in 155 cases that fifty-four excreted diphtheria bacilli. Beyer¹⁹⁰ also has high positive results, finding them even in cases where the patients harbor the bacilli in the tonsils. Freifeld¹⁹¹ reports a case of secondary cystitis in which the diphtheria bacilli were present for many months, treatment being without effect.

Complications.—Benesi¹⁹² describes three types of diphtheritic otitis; (a) primary diphtheria of the ear; (b) secondary diphtheria of the ear; (c) diphtheritic otitis associated with general infection. Jervis¹⁹³ reports a case of pulmonary abscess. Beyer¹⁹⁴ saw a case of fetid diphtheritic bronchitis with recovery. Schmidt¹⁹⁵ saw a case of bronchiectasis in which diphtheria bacilli were present in the sputum for two years. Stewart¹⁹⁶ reports a case of pulmonary embolism in which the initial attack, which was mild, became rapidly severe. Leede¹⁹⁷ describes four cases of postdiphtheritic hemiplegia. Reiche¹⁹⁸ shows that in eight cases of meningitis the infecting microorganism was never the diphtheria bacillus, being either the meningococcus, *B. Coli*, streptococcus, pneumococcus or staphylococcus. Dynkin¹⁹⁹ describes the necropsy findings in a case of cerebral involvement with aphasia, in which widespread softening was noted. Wolff²⁰⁰ saw a case of postdiphtheritic facial palsy following nasal diphtheria. According to Schuster,²⁰¹ certain strains of diphtheria bacilli may excrete a neurotropic toxin. Thus, three members of the family suffered with postdiphtheritic paralysis.

Therapy.—The intravenous therapy first suggested by von Behring in 1901 has been extensively practiced of late years, but little critical work has appeared with regard to its possible clinical advantage. Beyer²⁰² tried it in twenty-six cases and obtained the impression that

188. Koch, R.: *Deutsch. med. Wchnschr.*, 1912, xxxviii, 2358.

189. Conradi and Bierast: *Deutsch. med. Wchnschr.*, 1912, xxxviii, 1580.

190. Beyer, W.: *München. med. Wchnschr.*, 1913, ix, 240.

191. Freifeld, E.: *Berl. klin. Wchnschr.*, 1913, i, 1761.

192. Benesi, O.: *Wien. klin. Wchnschr.*, 1912, xxv, 1385.

193. Jervis, J. J.: *Brit. med. Jour.*, 1914, i, No. 2781, p. 859.

194. Beyer: *München. med. Wchnschr.*, 1913, lxi, 25.

195. Schmidt: *Berl. klin. Wchnschr.*, 1912, xlix, 2090.

196. Stewart, D.: *Lancet*, London, 1912, No. 4622, p. 866.

197. Leede, W. H.: *Ztschr. f. Kinderh.*, 1913, viii, 88.

198. Reiche, F.: *Ztschr. f. Kinderh.*, 1914, xi, 452.

199. Dynkin, A. L.: *Jahrb. f. Kinderh.*, 1913, lxxviii, Supplement 267.

200. Wolff, S.: *Jahrb. f. Kinderh.*, lxxvii, No. 2.

201. Schuster, P.: *Neurol. Centralbl.*, 1914.

202. Beyer, W.: *München. med. Wchnschr.*, 1913, ix, 1867.

the membrane disappeared more quickly when a subcutaneous injection was practiced, although its advantage was slight. Alber,²⁰³ on the other hand, is of the opinion that striking results were achieved in thirty-two very severe cases, in which the intravenous administration of serum was combined with intramuscular injections. Of these patients, but two died, even though it was necessary to do five tracheotomies. Fever dropped strikingly in two days at most, and the membrane seemed to come off more quickly. Only one case of serum rash followed. There were, however, eight cases of paralysis of the soft palate, but no general neuroparalysis. Park²⁰⁴ covers the subject of antitoxin administration and considers it from several aspects. Conclusions drawn from his animal experiments verify the observations of other observers; as, for example, the fact that a heterologous serum disappears from the circulation more rapidly than does a homologous serum. When given subcutaneously the maximum antitoxin content of the blood is not achieved until after forty-eight hours, although it lasts from two to three days. He feels that it is better to give one large dose than several small ones. Intravenous administration of serum is indicated in severe cases, 5,000 units in this way being equivalent to 20,000 subcutaneously. Woody²⁰⁵ discusses the effect of very large doses of antitoxin on the basis of mortality statistics. The following figures taken from hospital cases are as valuable as data of this kind can be:

Year	Cases	Deaths	Per Cent.	Dosage
1908.....	1426	127	8.55	Very small
1909.....	2153	144	6.69	Large
1910.....	1870	120	6.42	Larger than 1909
1911.....	1895	130	6.86	Smaller than 1909-1910
1912.....	1676	101	6.02	Larger doses

Nemms²⁰⁶ urges the use of the Besredka method of giving antitoxin and shows that the danger even with repeated antitoxin administration is very slight. Schibayama²⁰⁷ tried to avoid anaphylactic phenomena by the rectal administration of antitoxin, but he found that it did not give an appreciable passive immunity. The account of several experiences with the intralumbar administration of serum have appeared. Porak,²⁰⁸ in a case of severe postdiphtheritic paralysis, gave seven such treatments in as many days, with satisfactory results. Kleinschmidt,²⁰⁹ on the basis of laboratory experiments as to the firmness of union between toxin and brain tissue and the power of antitoxin to

203. Alber, K.: *Jahrb. f. Kinderh.*, 1914, lxxx, 312.

204. Park, W. H.: *Boston Med. and Surg. Jour.*, 1913, clxvii, 73.

205. Woody, S. G.: *Jour. Am. Med. Assn.*, 1914, lxiii, 861.

206. Nemms, M.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 740.

207. Schibayama, C.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 738.

208. Porak: *Bull. Soc. de pédiat. de Paris*, 1912, p. 314.

209. Kleinschmidt, H.: *Jahrb. f. Kinderh.*, 1912, lxxvi, 179.

separate such mixtures, urges this method of treatment, even though the experiments are disputed by Beyer.²¹⁰ Bingel²¹¹ interprets the vomiting which occurs in malignant diphtheria five or more days after the onset of the disease (when the local signs in the throat are moderate) as being of cerebral origin. He also gave the serum by injection into the lumbar space. Symptomatic improvement was noted, but the high mortality was not diminished. Weintraud also urges this form of treatment.

Krause and Becher²¹³ emphasize the fact that the curative action of diphtheria antitoxin does not depend necessarily upon its strength in vitro. There seems to be a variation of the avidity of different antitoxins for toxin.

The use of vaccine or bacterial substances in the treatment has been attempted with varying results. This method has been used chiefly in the case of carriers or in low grades of infections. Hewlett and Nankivell²¹⁴ used the method of McFadyen, which consists in the grinding, in the presence of intense cold, of the washed diphtheria bacilli and then passing the material through a Berkefeld filter. Results in active cases are not greater than by the method of serum administration. It is interesting to note that one patient was cured only after a necrotic turbinate in the nose had been removed.

Treatment of Carriers.—Petruschky found success in the treatment of carriers by vaccine made from bacilli killed by chloroform and washed free of toxin. Meyer²¹⁶ also had good results, especially in the treatment of nasal diphtheria in infants. Weil²¹⁷ reports the results in fifteen cases, in only six of which were they satisfactory. In these, however, the cultures remained permanently negative. He advises the use of large doses, up to 200,000,000.

It seems to me scarcely necessary to quote completely the literature which has appeared dealing with the "overriding" treatment of diphtheria carriers with staphylococcus cultures (Schlötz). Bissell²¹⁸ calls attention to some studies that he has made, unfortunately not published in full, which tend to show that the use of the staphylococcus spray may deceive the observer. This investigator finds that the "overriding" does not produce extermination of the bacilli in the fauces, but that in

210. Beyer, W.: *Jahrb. f. Kinderh.*, 1913, lxxvii, 65.

211. Bingel, C.: *Deutsch. Arch. f. klin. Med.*, 1911, civ, 370.

213. Krause and Becher: *Deutsch. med. Wchnschr.*, 1913, xxxix, 1081.

214. Hewlett and Nankivell: *Lancet*, London, 1912, No. 4638, p. 143.

216. Meyer, F.: *Ztschr. f. Kinderh.*, 1912, ii, 575.

217. Weil, A. L.: *Laryngoscope*, 1914, xxiv, 804.

218. Bissell, W. G.: *Jour. Am. Med. Assn.*, 1913, lxi, 1393.

the cultures taken the staphylococci tend to overgrow the diphtheria bacilli in the serum tube. De Witt²¹⁹ shows that there is no inherent antagonism between the diphtheria bacillus and the staphylococcus in culture. In animal experiments she also found that, as compared with the controls, in 40 per cent. of the cases the bacilli were gotten rid of more readily by this method, whereas, in 60 per cent. the result was the same. Many of the clinical articles which have appeared on this subject give only a small number of cases, without the careful control suggested as above. Rolleston²²⁰ found that there was nothing accomplished from this treatment in nasal cases. Lorenz and Ravenel²²¹ show, for example, that in one case in their series the patient became a carrier in three months after this treatment and that the reinfection was again "cured" by the use of spray. They also show that in several instances the cultures, which were negative, again became positive. Alden²²² comments on the different by-effects, such as fever, sore throat and edema of the face. He was satisfied with two negative cultures taken two days following the treatment. Ten Broeck²²³ uses the thallophytic fungus, *Achlya mascaris*, as a spray.

The fact that the diphtheria bacilli in carriers localize themselves either in the crypts of the tonsils or in the nasal tissues is being recognized more and more as a basis on which efficient treatment of these troublesome cases must be founded. Reference has been made to the work of Hewlett and Nankivell,²¹⁴ wherein mention is made of the necessity of removing a necrotic turbinate. Albert,²²⁴ after reviewing the methods, suggests that the crypts be cleaned out and treated with a strong antiseptic solution. Greene²²⁵ removes the tonsils and adenoids in bacillus carriers, preceding the operation with prophylactic doses of serum. Dreyfus,²²⁶ while reporting but one case, brings out a very valuable point. The patient described suffered with polyneuritis, chiefly sensory in character. The infection took place in June, the neuritis developing the month after. At the time of operation the antitoxin content of the blood was 0.10 unit per cubic centimeter. In spite of this, 2,000 units were given as an added precaution. The tonsils were found to contain pus, and the presence of diphtheria bacilli was easily demonstrated. Immediate improvement was noted and a complete recovery obtained after removal of the tonsils.

219. De Witt: Jour. Infect. Dis., 1912, x, 24.

220. Rolleston, J. D.: Brit. Jour. Child. Dis., 1913, x, 298.

221. Lorenz and Ravenel: Jour. Am. Med. Assn., 1912, lix, 690.

222. Alden, A. M.: Jour. Am. Med. Assn., 1913, lxi, 1876.

223. Ten Broeck, L. L.: Med. Rec., New York, 1914, lxxxv, 49.

224. Albert: Am. Pub. Health Jour., 1913, lxi, 1027.

225. Greene, J. B.: Boston Med. and Surg. Jour., 1913, clxviii, 912.

226. Dreyfus: Med. Klin., 1914, x, 970.

SCARLET FEVER

Epidemiology.—Striking advance has been made in recent years in the study of scarlet fever. As to the nature of the disease, Von Szontagh²²⁷ reviews his earlier experiences and statements and emphasizes his notion, without bringing out definite experimental evidence, that scarlet fever differs from tonsillitis only in the fact that it indicated a peculiar reaction on the part of the body to the infecting micro-organism. The circumstantial evidence which he relies on to bear out his very firm conviction is found in the frequency of the so-called idiopathic origin of cases without epidemic, the great variability of the rash, the variation in infectiousness, and the long infectivity of the purulent discharges from the nose and ears. He shows, for example, that the frequency of scarlet fever during the year in Budapest tends to remain at a more constant level throughout the year, than is the case in other diseases, such as measles, in which distinct seasonal variations are found.

The question of the existence of scarlet fever in Japan is discussed in a communication,²²⁸ and while it is not distinctly proved that scarlet fever does not exist, it seems quite certain that the disease is one of very great rarity or, if present, occurs in a form which is either different from the type we are accustomed to see, or is very difficult to recognize. The method of transmission by books is discussed by Nesbit.²²⁹ During an epidemic it seemed quite probable that the books from the public library played no part in the spreading of the disease. Fleas are blamed in the London letter²³⁰ for the transmission of scarlet fever. These parasites in London multiply during late summer and autumn, but are not so prolific in winter. The curve of the incidence of scarlet fever parallels this exactly.

The question of a familial predisposition to scarlet fever and especially to the complicating nephritis is a subject of discussion between Mathies²³¹ and Bode.²³² Using the statistical method, the former concludes that there is no distinctly peculiar familial disposition, stating that members of the same family need not have the same type of the disease and that there may often be several different streptococci complications in such a group. The latter, using the same method, finds just the reverse. Urszinji²³³ believes that in time of epidemics children should be subjected to routine throat gargles with an antiseptic solution.

227. Von Szontagh: *Jahrb. f. Kinderh.*, 1912, lxxvi, pp. 1 and 654.

228. *Jour. Am. Med. Assn.*, 1913, lix, 669.

229. Nesbit, O. B.: *Jour. Am. Med. Assn.*, 1912, lix, 1526.

230. London Letter: *Jour. Am. Med. Assn.*, 1914, lxii, 1183.

231. Mathies: *Jahrb. f. Kinderh.*, 1913, lxxviii, Supplement, 116.

232. Bode, P.: *Jahrb. f. Kinderh.*, 1914, lxxix, 438.

233. Urszinji, J.: *Pest. med.-chir. Presse*, 1913, p. 245.

Vaccine prophylaxis is urged by Watters,²³⁴ who uses the method of Gabritschewsky. Three injections of streptococcus vaccine were given at intervals of eight days to nurses who had not yet had scarlet fever. Of the fourteen not injected, five developed the disease; of the twenty-one injected, only one developed the disease. De Biehler,²³⁵ Krukowsky,²³⁶ and Czarkowsky,²³⁷ all used this method and found that of 128 cases only two developed the disease. Keifer and Ferry,²³⁸ in a rather small series also have a favorable impression of the value of this method of prophylaxis. Their vaccine contained both streptococcus and a so-called micrococcus "S." Several injections of about 200,000,000 organisms at intervals of from two to three days served to render efficient protection. Previous to the use of the vaccine a morbidity of 6 per cent. of those exposed was noted. None were affected while the vaccine was used, but the disease again appeared after ceasing to use it. Not only that, but the mortality and frequency of complications is asserted to have been diminished.

The return cases as a source of infection is discussed by Baginsky,²³⁹ after the matter had been brought up as a result of an English law suit. Sexton²⁴⁰ has observed sixteen return cases in three years and notes that they may occur even if there is no discharge from the eyes, the ears or the respiratory tract. They occur usually in the winter and are believed to be due to coryza developing. Wegmann²⁴¹ in thirty-two return cases found that eighteen were of the exudative type, and he believes that these children with their greater susceptibility to infections of the upper respiratory tract are more likely to harbor the infecting organisms. Higgins²⁴² believes that when the diphtheria bacillus has been present there is a greater tendency to a prolongation of the infectious stage beyond the ordinarily accepted period. An interesting instance of reinfection is reported by Jacobson.²⁴³ In a family of four all of whom had had scarlatina, which had been diagnosed by several physicians, the disease again developed.

Diagnosis.—The differentiation of scarlet fever from infectious erythema has long been known as being of the greatest difficulty. Any method which will be of assistance has been eagerly seized upon. Döhle²⁴⁴ reports further investigations dealing with leukocytic inclusion

234. Watters, W. H.: Jour. Am. Med. Assn., 1912, lxiii, 546.

235. De Biehler, M.: Arch. de méd. d. enfants, 1914, xvii, 193.

236. Krukowsky: Medycyna, 1914, xlix, 990.

237. Czarkowsky: Medycyna, 1914, xlix, 985.

238. Keifer, G. L., and Ferry, N. S.: Med. Rec., New York, 1914, lxxxv, 1846.

239. Baginsky, A.: Abstr., Jahrb. f. Kinderh., 1913, lxxvi, 473.

240. Sexton, L. A.: Arch. Pediat., 1913, xxx, 360.

241. Wegmann: Abstr., Jahrb. f. Kinderh., 1913, lxxviii, 474.

242. Higgins, T. S.: Brit. Jour. Child. Dis., 1912, x, 418.

243. Jacobson: Arch. de méd. d. enfants, 1914, xvii, No. 4.

244. Döhle: Centralbl. f. Bakteriöl., 1912, ??? 57.

bodies, which he described the year before. Kretschmer²⁴⁵ found these bodies in all early cases of scarlet fever, but found them also in diphtheria and septic diseases. Glomset²⁴⁶ found them often in health and obtained them artificially by shaking the blood. Schippers and de Lange²⁴⁷ found them in all cases of scarlet fever, but also in other diseases, especially of streptococcal origin. They produced them by injecting dogs with this micro-organism. Bongartz²⁴⁸ found them in typhoid, pneumonia and pertussis. Iskander Ahmed²⁴⁹ found them in German measles. Nicoll,²⁵⁰ however, missed them in this disease. Granger and Pale²⁵¹ missed them in the very severe cases of scarlet fever. They are not present in the so-called toxic rash. The value of these inclusion bodies in scarlet fever may be summed up by stating that they have only a negative diagnostic value; that is to say their absence speaks against a given rash being of scarlatinal origin. The Diazo reaction was suggested as a means of distinguishing between the serum rash and true scarlet fever. Woody and Kolmer²⁵² find that the Diazo reaction is as often positive in diphtheria as in scarlet fever and therefore is of no service. Schultz and Grote²⁵³ used the Abderhalden method, hoping to determine whether a ferment with a specific action upon the scarlatinal lymph glands existed. They found that the ferments obtained were not specific for such glands, but would digest lymph gland tissues in general.

An interesting diagnostic test has been put forward by Umber.²⁵⁴ Noting that urobilinogen appeared in the urine in many cases of scarlet fever, he suggested the use of an acid solution of paradimethylamidobenzaldehyde (Ehrlich's reagent) and found 96 per cent. positive results. Schelenz²⁵⁵ verifies these findings and shows a section of an acute interstitial hepatitis. He emphasizes the fact that the test is valid only when done on the freshly passed urine. Hesse²⁵⁶ also is of the opinion that the test is of value, and finds that it is necessarily coincident with the exanthem and that of course it can not be relied on alone for diagnosis. Gromski²⁵⁷ determined the presence of urobilinogen by means of the spectroscope. He found it to vary with the tem-

245. Kretschmer: *Deutsch. med. Wchnschr.*, 1912, xxxviii, 2163.

246. Glomset, D. L.: *Jour. Infect. Dis.*, 1912, xi, 468.

247. Schippers and de Lange: *Nederl. Tijdschr. v. Geneesk.*, 1913, 544.

248. Bongartz, H.: *Berl. klin. Wchnschr.*, 1912, xlix, 2124.

249. Ahmed, Iskander: *Berl. klin. Wchnschr.*, 1912, xlix, 1232.

250. Nicoll: *Arch. Pediat.*, 1912, xxix, 350, 416; *Ibid.*, 1913, xxx, 346.

251. Granger and Pale: *Brit. Jour. Child. Dis.*, 1913, x, 9.

252. Woody and Kolmer: *Arch. Pediat.*, 1912, xxix, 12.

253. Schultz, W., and Grote, L. R.: *München. med. Wchnschr.*, 1913, ix, 2510.

254. Umber, F.: *Med. Klin.*, 1912, viii, 322.

255. Schelenz, C.: *Med. Klin.*, 1913, ix, 622.

256. Hesse, O.: *Med. Klin.*, 1913, p. 294.

257. Gromski: *Abstr. Jahrb. f. Kinderh.*, 1914, lxxix, 383.

perature. Alimentary levulosuria could be produced by giving 40 to 60 gm. levulose. Jakobovicz²⁵⁸ found the Wassermann reaction positive in eighteen out of fifty-five cases. It did not become positive, however, until the end of the third week and occurred most often in the severe cases. Michael²⁵⁹ produced the so-called Rumpel-Lede phenomenon in 60 per cent. of healthy children by means of a blood pressure cuff, pressure of 60 mm. being applied for ten minutes. The spontaneous appearance of this phenomenon is discussed by Meyer,²⁶⁰ who found it in all cases of scarlet fever, and in some cases of measles, sore throat and pernicious anemia. It was not found in German measles or erythema multiforme. Kirsch²⁶¹ is of the opinion that the rash of scarlet fever is due to the action of the toxin upon the muscular element of the capillaries and that, in given cases, the damage may be of a more or less permanent character, leading to the so-called angioneuroses. In the disappearing scarlet fever eruption, he²⁶² finds at times that the tonus of the arteries and veins does not completely return to normal. During this period there are areas of pallor and also the appearance of persisting dilated capillaries. Hahn²⁶³ discusses surgical scarlatina and finds a more intense rash, but a milder course with rare complications, to be the rule. The enanthem is either absent or, if present, is very slight only. The point of entrance of the virus is the face or the mouth.

Rolleston²⁶⁴ has studied the blood pressure in scarlet fever and finds it to be subnormal in 25 per cent. of the cases, varying with the extent and duration of the initial attack. It is little over normal in the first week, but the reading diminishes toward the end of the disease. A very moderate hypertension, which is never extreme or of long duration, is occasionally encountered during the time of kidney complications. It may be concluded, therefore, that the systematic blood pressure readings are of little diagnostic or prognostic significance in themselves. The pronounced hypotension met with in adrenal insufficiency of course calls for adrenal medication. Pancreatitis as a complication of scarlet fever has been seen by Goldie.²⁶⁵ In this series of four cases reported (one followed diphtheria) the pancreas was palpable. The symptoms were chiefly abdominal pain and tenderness, rigidity, tremor, jaundice, vomiting and general malaise. Tixier and

258. Jakobovicz, B.: *Jahrb. f. Kinderh.*, 1914, lxxix, 215.

259. Michael, M.: *Arch. Pediat.*, 1912, xxix, 298.

260. Meyer, O.: *Deutsch. med. Wchnschr.*, 1912, xxxviii, 2019.

261. Kirsch, O.: *Ztschr. f. Kinderh.*, 1912, iv, 92.

262. Kirsch, O.: *Wien. klin. Wchnschr.*, xxvi, 1848.

263. Hahn, H.: *Monatsch. f. Kinderh.*, 1913, xii, 233.

264. Rolleston, J. D.: *Brit. Jour. Child. Dis.*, 1912, ix, 444.

265. Goldie: *Lancet*, London, 1912, No. 183, p. 1285.

Troisier²⁶⁶ discuss the pathologic findings in the pancreas and the adrenal and call attention to the difficulty in definitely diagnosing the condition, pancreatitis, *intra vitam*; abdominal pain is a prominent symptom. In adrenal involvement abdominal or lumbar pain, cardiovascular collapse, and tachycardia are present.

Complications.—Several interesting complications are noted. Silberstein²⁶⁷ reports a very rare complication—symmetrical gangrene of the skin. McCrick²⁶⁸ reports a case of purpura fulminans developing nineteen days after the onset of the disease, with fatal termination. Stevenson²⁶⁹ has a case of purpura hemorrhagica. Eichhorst²⁷⁰ reports a case of complicating erythema nodosa. Riddell²⁷¹ reports a case of necrosis of the vertebra following scarlet fever. Gangrene of the sinus pyrifermis has been encountered by Hecker.²⁷² Edgerly²⁷³ discusses the joint complications in scarlet fever, with particular reference to the purulent form. The ear complications are discussed by Borden.²⁷⁴ The middle ear is involved in 94 per cent. of fatal cases; the mastoid, in 26 per cent. Holmgren²⁷⁵ does not find that the high mortality is necessarily associated with the percentage of otitis media. In his series only 33 per cent. of the patients in the fatal cases had otitis. After the second year the tendency to otitis diminished. This complication may develop without fever. He believes, however, that permanent perforations are present in 40 per cent. of all cases of otitis and that the hearing is affected in 73 per cent. The earlier the otitis develops the worse the prognosis, although the mastoid involvement tends to be associated more often with a late otitis. Children with adenoids have more serious results when the complication develops. He favors local treatment of the throat. The hospital at Stockholm has its own attending otologist for treatment of these patients.

Kalser and Lowy²⁷⁶ have studied the variations in blood serum concentration. An increase in concentration has been noted in most cases and, therefore, is of no value in predicting nephritis. Fishbein²⁷⁷ has used the functional test with phenolsulphonephthalein, but draws no definite conclusions as to the value in prognosis. Schridde²⁷⁸ studied

266. Tixier and Troisier: *Arch. de méd. d. enfants*, 1912, xv, 321.

267. Silberstein, L.: *Jahrb. f. Kinderh.*, 1912, lxxv, 350.

268. McCrick, R.: *Brit. Jour. Child. Dis.*, 1912, No. 110, p. 154.

269. Stevenson, E. C.: *West. Med. Rev.*, 1912, xvii, No. 3.

270. Eichhorst, H.: *Med. Klin.*, 1914, x, 1045.

271. Riddell, D. F.: *Glasgow Med. Jour.*, 1913, lxxviii, No. 6.

272. Hecker, T.: *St. Petersburg. Med. Ztschr.*, xxxvii, No. 18.

273. Edgerly, E. T.: *Jour. Iowa State Med. Soc.*, 1912, ii, No. 3.

274. Borden, C. R. C.: *Boston Med. and Surg. Jour.*, 1913, clxviii, 221.

275. Holmgren, G.: *Otolaryngologiska*, 1912; abstr., *Jahrb. f. Kinderh.*, 1913, lxxviii, 485.

276. Kalser and Lowy: *Deutsch. Arch. f. klin. Med.*, 1914, cxvi, 82.

277. Fishbein, M.: *Jour. Am. Med. Assn.*, lxi, 1368.

278. Schridde, H.: *Beitr. z. path. Anat. u. z. allg. Path.*, 1912, lv, 345.

the pathology of the kidneys in scarlatina and found that the characteristic changes consist in an enormous heaping up of lymphocytes in the capillaries of the medulla. Later, plasma cells, eosinophils and mast cells are found. There are no polymorphonuclears and no streptococci.

Several attempts have been made to prevent nephritis by dietary treatment. De Biehler²⁷⁹ followed two groups of cases. In the first a milk diet was ordered, and but 2.4 per cent. developed nephritis, while among those given meat and mixed diet 5.3 per cent. showed this complication. Gerstley²⁸⁰ comes to the opposite conclusion in following 306 patients, of whom half were given milk and one half mixed diet with meat. Not only were there no bad results, but the anemia so frequently following scarlet fever was prevented in part. Brückner²⁸¹ in 241 cases is also convinced of the fact that the diet does not play a part in the development of the disease. Bell²⁸² makes an interesting attempt in accordance with the idea of Fisher to prevent nephritis, namely, the administration of water and alkali in addition to the usual bed and dietary treatment. He used potassium citrate and sodium bicarbonate in the first ten days of the disease. Of 388 cases, but 2 per cent. developed this complication. The effectiveness of this treatment can be gaged by referring to the article of de Biehler.²⁸³ Rosenfeld²⁸⁴ examined ninety-three patients who had had scarlet fever, of whom fifty-two showed albuminuria at the time of discharge from the hospital. No single severe chronic nephritis was found. Orthostatic albuminuria was found in eight cases and twenty-eight showed a simple albuminuria. Formed elements in small number were found in but six cases.

Therapy.—The finding of a positive Wassermann test in a certain number of cases of scarlet fever has induced some observers to attempt the use of salvarsan for therapeutic purposes. Klemperer and Woita²⁸⁵ administered this drug in sixty cases. The mortality was 8.3 per cent. Nephritis developed in 25 per cent. These figures speak for themselves. Glaser²⁸⁶ used the drug in forty-two cases and found it to be of beneficial influence only in severe throat conditions, and a critical fall in temperature was observed at times. It has no influence on complications or on toxic cases. Lenzmann²⁸⁷ treated forty-seven

279. De Biehler: *Arch. de méd. d. enfants*, 1912, xv, 739.

280. Gerstley, J. R.: *Monatsch. f. Kinderh.*, 1913, xii, 121.

281. Brückner: *Fortschr. d. Med.*, 1912, 1.

282. Bell, A. J.: *Am. Jour. Med. Sc.*, 1912, cxliv, 669.

283. De Biehler: *Arch. de méd. d. enfants*, 1912, xv, 579.

284. Rosenfeld, J.: *Ztschr. f. Kinderh.*, 1912, iv, 265.

285. Klemperer and Woita: *Therap. d. Gegenw.*, 1912, liii, 198.

286. Glaser: *Deutsch. med. Wchnschr.*, 1914, xl, 1760.

287. Lenzmann: *Therap. d. Gegenw.*, 1914, Iv, 243.

patients having scarlet fever in a severe form with neosalvarsan, of whom but two died. This was given intramuscularly daily or every second day. The dosage was from 0.15 gm. to 0.3 gm. for children. The maximum dose in three days was never over 0.8 gm.

Reiss and Jungmann²⁸⁸ suggested the use of the serum of convalescents for treatment. The blood was obtained from scarlet fever patients during the third or fourth week. From 50 to 100 c.c. were given by intravenous injection in twelve cases with two failures, these being in a case of sepsis and in a case which turned out to be not scarlet fever. The ten cases were strikingly improved. The temperature fell within four hours, an average lowering of five degrees being attained. The pulse rate also became lower. It was most striking to see how delirious and toxic children would seem almost normal the morning after the injection. It had no effect, however, on secondary bacterial infections. Rowe²⁸⁹ found no difference between serum obtained from patients who had not had scarlet fever and serum from convalescents. He used from 40 to 50 c.c. intravenously and his results were in the main confirmatory of those cited above. Moog²⁹⁰ also found excellent results from human normal serum and believes that in the case of Moser's antistreptococcus serum the good effect obtained was due to the serum as such. Koch²⁹¹ reports twenty-two patients treated with convalescent serum by intravenous injections, 100 c.c. being used. Only bacterial complications were unaffected, while a beneficent influence on the disease was otherwise unmistakable. Barker,²⁹² apparently, independently of the above writers, used blood serum of immunes for the treatment in malignant septic cases. From 4 to 8 c.c. of the human serum hypodermically were given. No striking results were obtained. Prinzing²⁹³ noted that horse serum was not a satisfactory substitute for human serum. The critical fall in temperature did not follow its use and the symptoms were not so strikingly affected. Schultz²⁹⁴ found that the effect of human serum in scarlet fever was not due to the lipoid content, but with the non-treated serum, however, a critical fall in temperature could be produced. There are still some communications dealing with the use of the Moser serum. Schick²⁹⁵ found some improvement produced in toxic patients, while those in whom the bacteria themselves produce the symptoms were unaffected. He believes that the failures hitherto

288. Reiss and Jungmann: *Deutsch. Arch. f. klin. Med.*, 1912, cv, 70.

289. Rowe, C.: *Med. Klin.*, ix, 1978.

290. Moog: *Therap. Monatsh.*, 1914, p. 37.

291. Koch, R.: *München. med. Wehnschr.*, 1913, ix, 2611.

292. Barker, W. S.: *Arch. Pediat.*, 1914, xxxi, 599.

293. Prinzing, F.: *Med. Klin.*, 1914, x, 931.

294. Schultz, W.: *Deutsch. Arch. f. klin. Med.*, 1914, cxv, 627.

295. Schick, R.: *Therap. Monatsh.*, 1912, xxvi, 258.

reported may have been due to the small dosage or to a weak serum. Lewkowicz²⁹⁶ used an antistreptococcal serum in thirty cases, using twenty cases as controls. No effect was noted on the purely scarlatinal symptoms. The bacterial complications are not prevented, although they were surely improved. The Milne⁵⁹ treatment referred to under measles is commented on by Kretschmer,²⁹⁷ who first calls attention to the fact that this method of treatment was first suggested by Curgenven in 1890. Kretschmer finds that it has little protective prophylactic value and did not prevent complications. Koerber²⁹⁸ attempted to determine the efficiency of the Milne method by comparing the number of return cases, and he found there was no appreciable difference in the number. He is struck with the fact, however, that all complications in the eucalyptus series were less than in the controls. Only one half as many cases of nephritis developed in the treated series as in those nontreated. Schultze and Goldberger²⁹⁹ used the vaccine treatment as well as the Milne treatment. Their figures are rather suggestive in homes where better conditions might have been expected. Of 354 controls, a mortality of 3 per cent. was encountered, whereas among 128 patients in the slums who were subjected to this treatment the mortality was but 1.5 per cent. Complications were also less frequently observed in the treated patients.

Langauer,³⁰⁰ believing that the tonsils play an almost important rôle in scarlet fever, also believes in their local treatment. He used 10 per cent. hydrogen peroxid, 60 per cent. alcohol and 2 per cent. collargol in glycerin. When a membrane was present he removed this mechanically. Paoloantonio has found what seems to him a most efficient treatment for scarlatinal nephritis. In thirty cases the oral administration of from 10 to 20 drops of epinephrin (1 to 100) controlled the hematuria and edema and prevented the further development of the disease. Diuresis was increased and edema diminished.

296. Lewkowicz, X.: *Monatschr. f. Kinderh.*, 1912, x, 676.

297. Kretschmer, M.: *München. med. Wchnschr.*, 1912, lix, 1809.

298. Koerber: *München. med. Wchnschr.*, 1912, lix, 581.

299. Schultze and Goldberger: *Med. Rec.*, New York, 1914, lxxxv, 931.

300. Langauer, K.: *Pest. med.-chir. Presse*, 1913, p. 124.

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CORRECTION

In the July issue, p. 30, the heading "Electrocardiographic Studies of Congenital Heart Disease, Hugh McCulloch, Assistant in Pediatrics, George Washington University Medical School, Washington, D. C.," should have been "Assistant in Pediatrics, Washington University Medical School, St. Louis."

SCARLET FEVER, MORBIDITY AND FATALITY

BASED ON SEVERAL MILLION CASES *

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Certain families are more susceptible to scarlet fever than others. Physicians in active practice in contagious hospitals and elsewhere are familiar with this fact, because all the children in some families have the disease, whereas the rule is for but one or two of a number of brothers and sisters exposed to have scarlet fever. Besides this, physicians know that certain types of children—fat, flabby, overnourished and pasty children—bear the disease badly, and this gives rise to the knowledge that there is a variation in individual susceptibility. Could these differences in family and individual susceptibilities account for differences in fatality between different small epidemics of scarlet fever? Suppose that large collections of cases in various parts of the world were studied and compared, would it be found, with all types of individuals and families included, that scarlet fever after all was a fairly uniform disease, attacking year in and year out an average number of children, of whom an average number could be regularly expected to die in a fairly uniform proportion?

A study of these and similar questions by means of board of health statistics was suggested to me by Dr. John Howland for the epidemic diseases of childhood. Starting out with all the reportable diseases, it was found that scarlet fever was the one which admitted of such investigation with the greatest satisfaction, because it is and has been for some time generally well reported and has undergone little change in treatment, and also because it can usually be readily diagnosticated.¹ Diphtheria has had its specific treatment, which has tremendously influenced the figures. Measles, whooping cough and chickenpox are often so mild and so matter of course that a good proportion of cases are passed through without a call for a medical attendant, and remain unknown to the authorities. Difficulties of nice diagnosis rule out

* Submitted for publication May 22, 1916.

1. The error in diagnosis in New York City in 1914 was 1.6 per cent.

cerebrospinal meningitis from such a study, and infantile paralysis is too recent a disease in health office figures to make its study worth while.

Notification of contagious diseases is not a very old requirement and has but recently become general. Its value has become widely recognized, and severe penalties for failure by a physician to report a case of scarlet fever and constant watchfulness on the part of the authorities have resulted in adequate notifications in the main. The value of a study such as the present one is dependent upon the com-

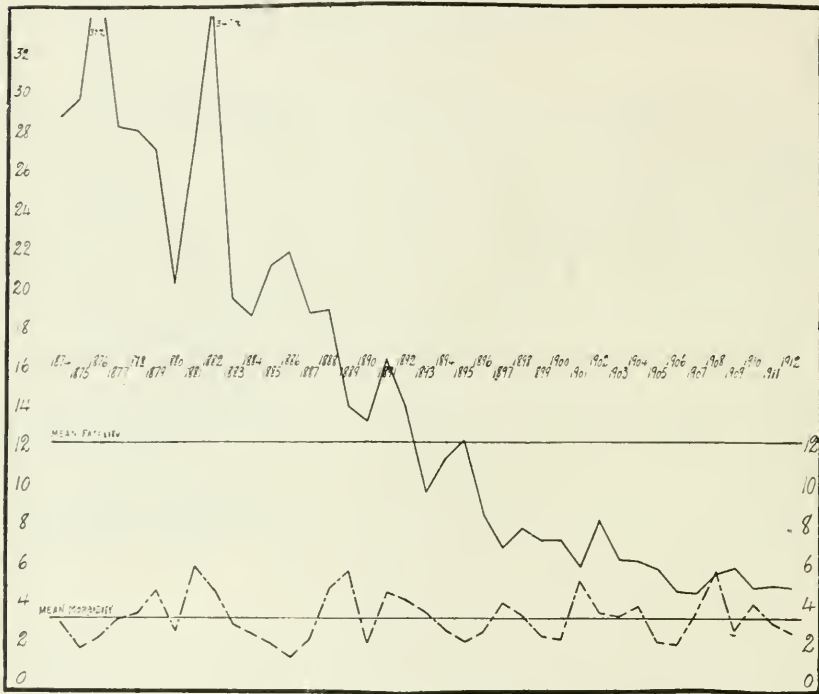


Fig. 1.—Morbidity and case fatality in New York for thirty-nine years, from 1874 to 1912, there being 229,071 cases, with 27,889 deaths, a case fatality of 12.2 per cent., and a morbidity rate of 3.2 per 1,000 population. The solid lines in Figures 1 to 12, inclusive, show the number of deaths per 100 cases; the broken line shows the number of cases per 1,000 population.

pleteness of the work of practicing physicians in making these reports. We know that all cases are not reported. With scarlet fever the very mild cases, which are unrecognized, and the very severe ones, in which the patients die without scarlet fever being given as the cause of death, balance to some degree, so that it is believed that the fatality figures obtained for this study give an approximately accurate idea of true conditions. Some health officials in their reports twenty-five or thirty

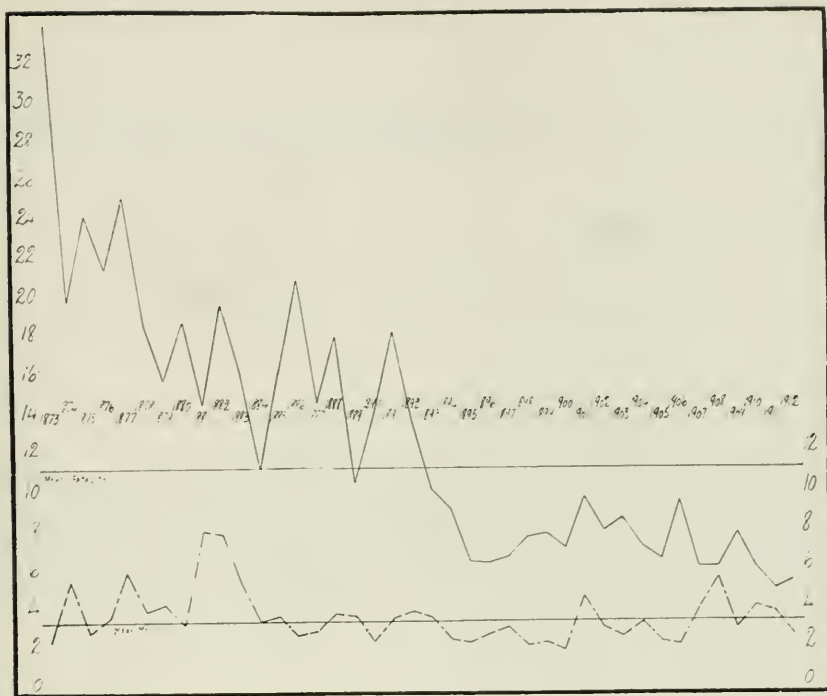


Fig. 2.—Morbidity and case fatality in Brooklyn for forty years, from 1873 to 1912, there being 122,928 cases with 13,492 deaths, a case fatality of 11 per cent., and a morbidity rate of 3.2 per 1,000 population.

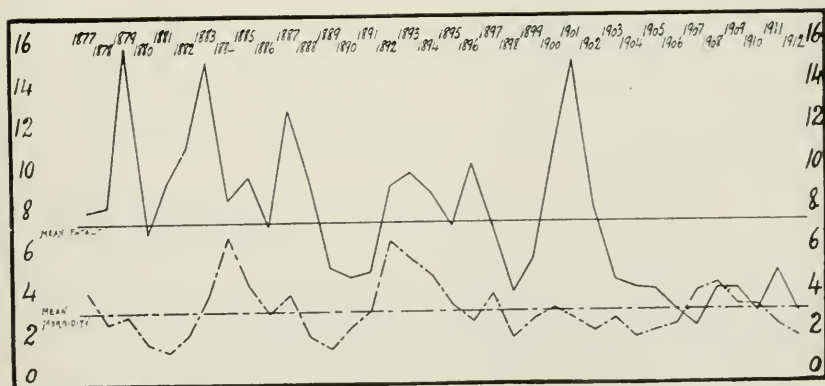


Fig. 3.—Morbidity and case fatality in Boston for thirty-six years, from 1877 to 1912, there being 52,246 cases and 3,755 deaths, a case fatality of 7.2 per cent., and a morbidity rate of 2.9 per 1,000 population.

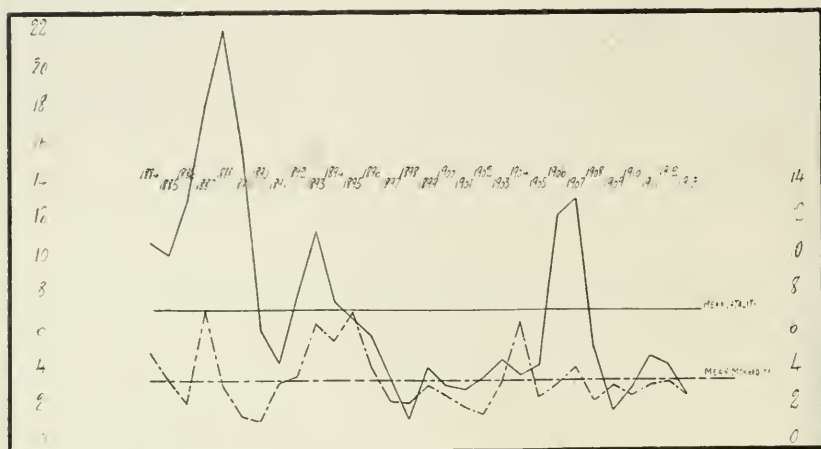


Fig. 4.—Morbidity and case fatality in Providence for thirty years, from 1884 to 1913, there being 16,135 cases with 1,141 deaths, a case fatality of 7.1 per cent, and a morbidity rate of 3.2 per 1,000 population.

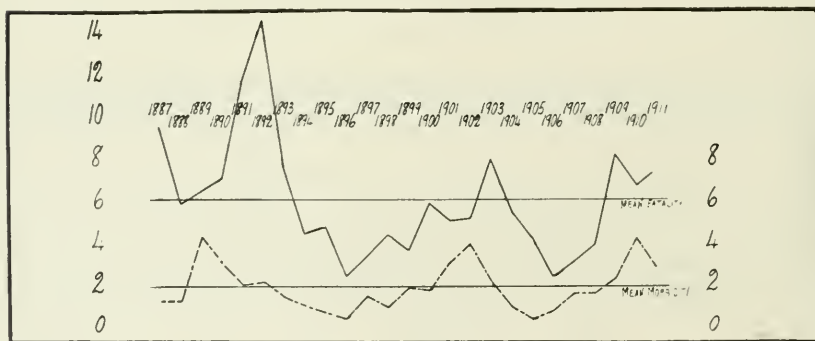


Fig. 5.—Morbidity and case fatality in St. Louis for twenty-five years, from 1887 to 1911, there being 27,213 cases with 1,625 deaths, a case fatality of 6 per cent, and a morbidity rate of 1.9 per 1,000 population.

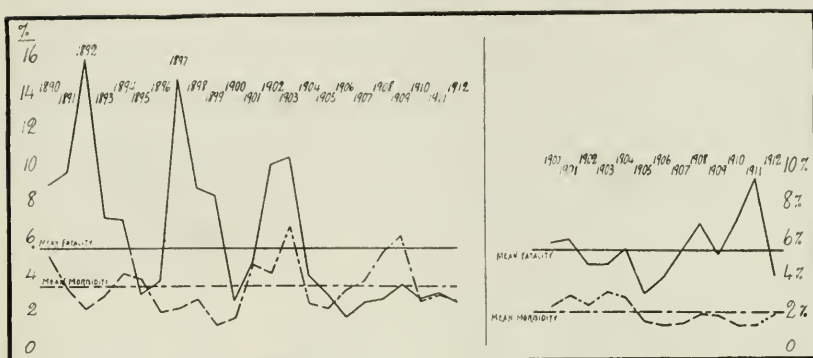


Fig. 6.—Morbidity and case fatality: at the left, in Nuremberg for twenty-three years, from 1890 to 1912, there being 18,657 cases with 1,003 deaths, a case fatality of 5.4 per cent. and a morbidity rate of 3.3 per 1,000 population; at the right, in Philadelphia for thirteen years, from 1900 to 1912, there being 35,204 cases with 1,876 deaths, a case fatality of 5.2 per cent. and a morbidity rate of 1.9 per 1,000 population.

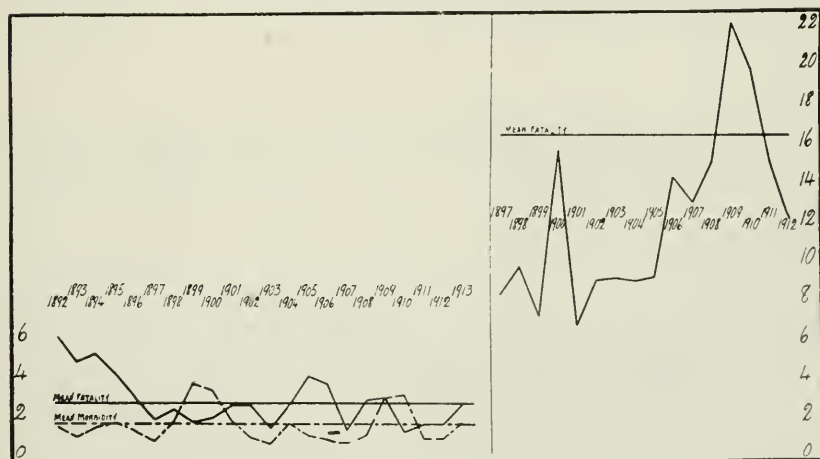


Fig. 7.—Morbidity and case fatality: at the left, in Washington, D. C., for twenty-two years, from 1892 to 1913, there being 9,476 cases with 238 deaths, a case fatality of 2.5 per cent. and a morbidity rate of 1.5 per 1,000 population; at the right, in Japan for sixteen years, from 1897 to 1912, there being 8,882 cases with 1,452 deaths, a case fatality of 16.3 per cent.

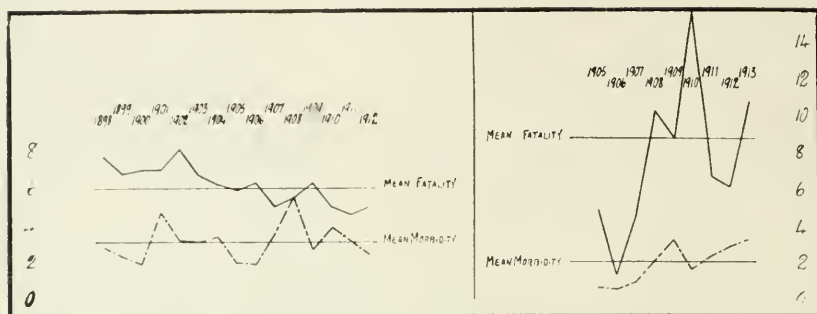


Fig. 8.—Morbidity and case fatality: at the left, in Greater New York, for fifteen years, from 1898 to 1912, there being 192,710 cases with 11,576 deaths, a case fatality of 6 per cent. and a morbidity rate of 3.1 per 1,000 population; at the right, in Montreal for nine years, from 1905 to 1913, there being 7,820 cases with 684 deaths, a case mortality of 8.7 per cent. and a morbidity rate of 2.1 per 1,000 population.

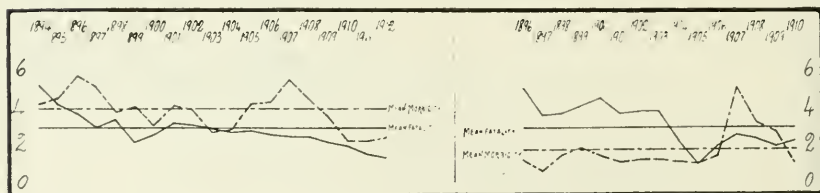


Fig. 9.—Morbidity and case fatality: at the left, in London, for nineteen years, from 1894 to 1912, there being 335,949 cases with 9,921 deaths, a case fatality of 3 per cent. and a morbidity rate of 3.9 per 1,000 population; at the right, in Paris, for fifteen years, from 1896 to 1910, there being 72,189 cases with 2,142 deaths, a case fatality of 3 per cent. and a morbidity of 1.8 per 1,000 population.

years ago spoke confidently on the adequacy of registration as far as scarlet fever cases were concerned. Even at the present day notification is inadequate in some countries. It is curious that such a state as Prussia, with its great complexity of laws, has had no compulsory notification law. The law in operation dates back to 1835 and provides that notification shall be made when scarlet fever is "particularly numerous or particularly malignant." For my purposes, therefore, the figures from Prussia are useless, no attempt being made there to report all cases. In Norway reporting has been excellent and the writer

has brought certain tables in Johannessen's classic work² down to date.

Morbidity and fatality rates are based on the number of cases and deaths reported during a calendar year, and not infrequently the figures of epidemics have been broken into, but it is believed that the treatment of numbers of years together has compensated for this.

In all, something over seven million cases have been collected, but for various

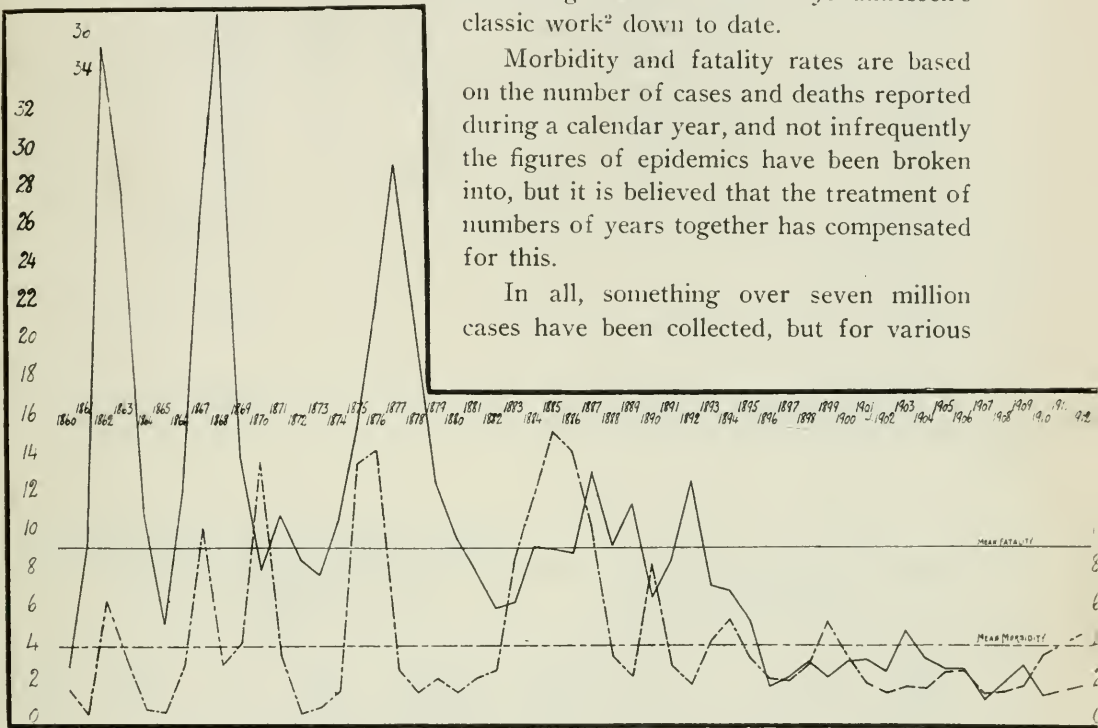


Fig. 10.—Morbidity and case fatality in Christiania for fifty-three years, from 1860 to 1912, there being 26,993 cases with 2,433 deaths, a case fatality of 9 per cent. and a morbidity rate of 3.8 per 1,000 population.

reasons some of these have had to be put aside, only those being retained concerning which it was believed that cases and deaths were well reported. Among approximately 2,000,000 cases there were 104,500 deaths, which gives a case fatality of $5\frac{1}{4}$ per cent., while the morbidity rate was 3.9, that is, about four persons in each 1,000 inhabi-

2. Johannessen: Die epidemische Verbreitung des Scharlachfiebers in Norwegen, Kristiania, 1884.

TABLE 1.—MORBIDITY AND CASE FATALITY—

Place	Period as a Whole						
	Time	Number of Years	Annual Populations (Aggregate)	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases
Eight American cities.....	1873-1913	41	177,047,815	2.8	500,093	50,700	10.1
Paris.....	1896-1910	15	40,070,803	1.8	72,189	2,142	3.0
Nuremberg.....	1890-1913	22	5,650,000	3.3	18,657	1,003	5.4
Norway.....	1867-1910	44	2.5	233,587	18,556	7.9
Norway.....	(1880-1910)	(31)	(11,689,508)	(2.5)	(162,592)	(9,349)	
Russian Empire.....	1893-1910	14	2.0	3,793,453	845,641	22.3
England and Wales.....	1892-1911	17	268,253,879	4.6	1,231,018	41,192	3.3
Prussia.....	1902-1912	11	787,476	59,079	7.5
Italy.....	1888-1910	23	428,541	93,094	21.7
Japan.....	1897-1912	16	8,882	1,452	16.3
Grand total	7,073,896
Total, exclusive of Russia, Japan, Italy and Prussia			2,055,544	113,593	5.5
Total, exclusive of Russia, Japan, Italy and Prussia, also Norway between 1867 and 1879.....			502,712,005	3.9	1,984,549	104,386	5.26

TABLE 2.—MORBIDITY AND CASE FATALITY OF—

Place	Period as a Whole						
	Time	Number of Years	Annual Populations (Aggregate)	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases
Boston.....	1877-1912	36	18,051,007	2.9	52,246	3,755	7.2
Providence.....	1884-1913	30	5,105,611	3.2	16,135	1,141	7.1
New York (old).....	1874-1912	39	71,852,353	3.2	229,071	27,889	12.2
Brooklyn.....	1873-1912	40	38,492,166	3.2	122,928	13,492	11.0
St. Louis.....	1887-1911	25	14,456,089	1.9	27,213	1,625	6.0
Philadelphia.....	1900-1912	13	18,862,594	1.9	35,204	1,876	5.3
Washington.....	1892-1913	22	6,505,482	1.46	9,476	238	2.5
Montreal.....	1905-1913	9	3,722,423	2.1	7,820	684	8.7
Total.....		177,047,815	2.82	500,093	50,700	10.1

—OF SCARLET FEVER IN VARIOUS COUNTRIES

Year of Maximum Fatality					Year of Minimum Fatality				
Year	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases	Year	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases
....
1896	1.3	3,283	170	5.1	1905	1.1	2,952	43	1.1
1892	2.1	321	51	15.8	1906	3.1	941	15	1.6
1877	1.8	7,850	1,183	15.1	1910	1.7	4,092	80	2.0
1904	2.3	323,488	126,904	39.0	1901	2.2	294,268	34,127	11.5
1894	4.3	53,045	2,514	4.7	1911	5.4	104,617	1,871	1.8
1909	91,512	8,455	9.2	1911	80,660	5,114	6.4
1888	4,532	9,050	200.0(1)	1909	32,010	2,703	8.4
1909	1,537	337	22.0	1901	46	3	6.5

—SCARLET FEVER IN EIGHT AMERICAN CITIES

Year of Maximum Fatality					Year of Minimum Fatality				
Year	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases	Year	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases
1879	2.7	951	149	15.7	1907	3.8	2,359	49	2.1
1888	2.9	361	79	21.9	1898	2.0	322	4	1.2
1876	2.2	2,406	891	37.0	1907	3.7	9,389	421	4.5
1873	2.1	930	314	33.8	1911	3.6	6,136	295	4.8
1892	2.1	1,056	153	14.5	1896	0.4	252	6	2.4
1911	1.2	1,928	179	9.3	1905	1.4	1,992	57	2.9
1892	1.3	338	20	5.9	1910	3.0	1,001	11	1.1
1910	1.7	756	118	15.6	1906	0.6	210	3	1.4
....

—NUMBER OF CASES OF SCARLET FEVER PER 1,000 POPULATION

1891	1892	1893	1894	1895	1896	1897	1898	1899	1900	1901	1902	1903	1904	1905	1906	1907	1908	1909	1910	1911	1912	1913	Aver. %
4.5	4.1	3.3	2.6	2.0	2.5	4.0	3.4	2.3	2.1	5.1	3.5	3.3	3.8	2.0	1.9	3.7	5.6	2.6	4.0	3.0	2.5	...	3.2
3.2	3.6	3.3	2.2	2.0	2.4	2.8	1.9	2.0	1.6	4.3	2.8	2.3	3.0	2.1	1.9	3.7	5.3	2.7	3.9	3.6	2.4	...	3.2
2.9	6.3	5.4	4.6	3.2	2.4	3.7	1.6	2.5	3.0	2.5	1.9	2.5	1.6	1.9	2.2	3.8	4.2	3.2	3.1	2.2	1.6	...	2.9
3.0	3.4	6.2	5.3	6.8	3.9	2.1	2.0	2.9	2.4	1.8	1.4	3.1	6.3	2.3	3.0	3.9	2.1	2.9	2.4	2.9	3.1	2.4	3.2
2.0	2.1	1.4	1.0	0.7	0.4	1.4	0.9	1.8	1.7	3.0	3.9	2.2	1.0	0.4	0.8	1.6	1.6	2.3	4.2	2.8	1.9
...	0.7	0.6	1.0	2.1	3.3	1.7	2.4	2.7	3.3	2.1
...	2.2	2.8	2.3	3.0	2.7	1.4	1.2	1.3	1.8	1.7	1.2	1.2	1.8	...	1.9
...	1.3	0.8	1.3	1.5	1.1	0.6	1.6	3.5	3.2	1.7	0.8	0.5	1.5	0.9	0.7	0.5	0.9	2.8	3.0	0.8	0.8	1.6	1.5
3.2	2.1	2.8	4.0	3.7	1.9	2.1	2.6	1.2	1.6	4.5	4.0	6.6	2.4	2.1	3.1	3.6	5.1	6.1	2.5	2.8	2.5	...	3.3
2.8	1.8	4.0	5.2	3.2	2.1	2.0	2.8	5.1	3.1	1.9	1.4	1.7	1.6	2.4	2.5	1.3	1.4	1.7	3.3	...	4.4	...	3.8
...	2.8	2.3	1.9	4.7	3.2	3.1	3.4	2.0	1.9	3.6	5.5	2.7	3.9	3.1	2.4	...	3.1
...	1.3	0.7	1.5	1.9	1.5	1.2	1.3	1.3	1.2	1.1	1.5	5.1	3.3	2.8	1.1	1.8
...	4.2	4.5	5.7	5.1	3.8	4.1	3.1	4.1	3.9	2.7	2.9	4.2	4.3	5.5	4.5	3.6	2.3	2.3	2.5	...	3.9
2.3	1.4	1.7	3.7	3.0	3.1	2.1	1.9	2.3	2.5	2.2	1.9	1.6	1.3	2.1	1.7	1.2	1.7	2.3	1.7	2.5
...	5.4	6.9	4.3	4.3	5.8	4.8	3.9	4.7	4.4	4.1	4.0	4.1	4.2	4.3	4.6	4.6	...	5.4	4.6
...	...	1.2	1.7	1.7	1.3	1.5	1.5	1.9	2.0	2.2	1.8	2.0	2.3	2.7	2.8	2.4	1.9	2.7	3.2	2.0

—NUMBER OF DEATHS PER 100 CASES OF SCARLET FEVER

1891	1892	1893	1894	1895	1896	1897	1898	1899	1900	1901	1902	1903	1904	1905	1906	1907	1908	1909	1910	1911	1912	1913	Aver. %
16.4	13.9	9.6	11.3	12.3	8.5	6.8	7.8	7.2	7.2	5.8	8.2	6.2	6.1	5.7	4.6	4.5	5.5	5.8	4.8	4.9	4.8	...	12.2
18.0	13.4	9.9	8.9	6.2	6.1	6.4	7.4	7.6	6.9	9.5	7.8	8.4	7.0	6.3	9.3	5.9	5.9	7.6	5.9	4.8	5.2	...	11.0
4.8	8.9	9.6	8.6	7.1	10.0	7.0	3.8	5.4	10.6	15.0	7.8	4.4	4.0	3.9	2.9	2.1	3.9	3.9	2.8	4.8	2.8	...	7.1 ^N
4.2	7.8	11.2	7.4	6.5	5.6	3.4	1.2	3.9	2.6	2.7	3.5	4.3	3.5	4.0	12.0	12.9	4.9	1.6	2.8	4.5	4.0	2.4	7.1
11.5	14.5	7.5	4.4	4.7	2.4	3.3	4.3	3.6	5.8	5.0	5.1	7.9	5.4	4.2	2.4	3.1	3.9	8.1	6.7	7.5	6.0
...	4.9	1.4	4.6	10.2	8.7	15.6	6.7	6.1	10.7	8.7
...	5.7	5.9	4.5	4.5	5.4	2.9	3.8	5.3	6.8	5.1	7.0	9.3	3.9	...	5.3
...	5.9	4.6	5.0	4.0	2.8	1.7	2.2	1.6	1.8	2.4	2.4	1.3	2.4	3.9	3.5	1.2	2.7	2.8	1.1	1.5	1.5	2.5	2.5
9.6	15.8	7.1	7.0	2.9	3.6	14.6	8.7	8.3	2.5	3.7	10.0	10.4	3.9	2.9	1.6	2.4	2.6	3.4	2.6	2.9	2.4	...	5.4
8.3	12.5	7.0	6.7	5.2	1.7	2.2	3.0	2.2	3.0	3.1	2.5	4.6	3.2	2.6	2.6	1.0	1.9	2.8	1.2	...	1.7	...	9.0
...	7.7	6.8	7.0	7.0	8.1	6.7	6.2	5.9	6.3	5.0	5.5	6.3	5.0	4.6	5.0	...	6.6
...	5.1	3.6	3.5	4.1	4.5	3.7	3.8	3.8	2.3	1.1	2.0	2.6	2.4	2.0	2.3	3.0
...	5.2	4.2	3.7	3.0	3.4	2.2	2.6	3.2	3.1	2.9	2.7	2.8	2.6	2.5	2.5	2.2	2.0	1.6	1.4	...	3.0
6.3	7.3	5.7	3.7	3.9	3.5	3.6	2.7	2.6	3.2	2.4	2.4	3.3	2.4	2.7	2.0	2.1	2.2	2.6	2.0	...	1.7	...	7.9
...	4.5	4.4	4.7	4.1	4.0	4.0	3.7	3.2	3.4	3.4	3.1	3.3	2.9	2.5	2.6	2.6	...	1.8	3.3
...	...	15.6	16.7	16.4	13.9	13.2	12.1	12.9	12.2	11.5	...	35.4	39.0	27.7	...	28.1	28.2	22.3
...	8.1	9.5	7.0	15.6	6.5	8.8	8.9	8.8	9.0	14.1	12.8	14.9	22.0	19.7	15.0	12.1	...	16.3

tants had scarlet fever, of whom one person in twenty died (Tables 1 and 2).

Susceptibility of Communities.—Comparison of the incidence of the disease in one locality with that in another is expressed in terms of the number of cases per 1,000 inhabitants, or the morbidity rate. Thus, in the thirty-nine years 1874-1912, there were reported in former New York 229,071 cases of scarlet fever (Fig. 1). From the sum of the annual populations of New York for this period, its mean morbidity rate for scarlet fever was found to be 3.2 per 1,000, which means that during these thirty-nine years, an annual average of 3.2 persons per 1,000 inhabitants had this disease.

Without enumerating the periods, which may be seen by reference to Tables 1, 2 and 3, and Figures 1 to 12, the mean morbidity rate for England and Wales was found to be 4.6; for London, 3.9; Nuremberg, 3.3; for the eight American cities, 2.8; Norway, 2.5;

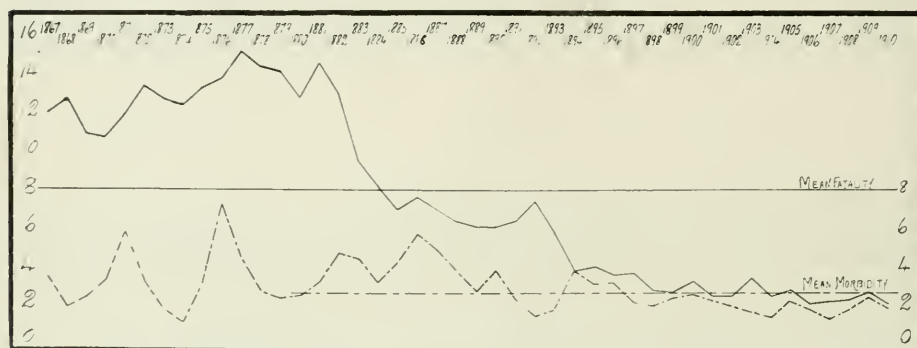


Fig. 11.—Morbidity and case fatality in Norway for forty-four years, from 1867 to 1910, there being 233,587 cases with 18,556 deaths, a case fatality of 7.9 per cent. and a morbidity rate of 2.5 per 1,000 population.

and Paris, 1.8 per 1,000. England had more scarlet fever than any of the other places studied. London has had more than twice as many cases per 1,000 inhabitants as Paris, while Greater New York has occupied a position between the two, with a mean morbidity rate since 1898 of 3.1 per 1,000. The mean morbidity rates of four American cities, over periods of from thirty to forty years were almost identical, being 3.2 for New York, Brooklyn and Providence, and 2.9 for Boston. St. Louis and Philadelphia had identical morbidity rates of 1.9; Washington, 1.5; and Montreal, 2.1 per 1,000. A marked difference in the incidence of scarlet fever in different localities is therefore present. In large cities the disease may be abundant in some parts and slight or absent in others; in London

this is continuously so. In only four of forty years was the incidence of scarlet fever in New York and Brooklyn the same, at times it differed widely, and yet their mean morbidity rates for the entire forty years were identical. (Further illustrations may be seen in Table 3.)

Fatality in Different Localities.—In comparing mortalities of different places it is done in terms of percentage, or deaths per 100 cases (Table 4 and Figs. 1 to 12). It is necessary to compare simultaneous years or periods of years. The mean case fatality of Greater New York since 1898 is 6 per cent., while London and Paris during practically the same period have had only half the case fatality, namely, 3 per cent.; Washington, 2.5 per cent.; Philadelphia, 5.3 per cent. Since 1892 the mean case fatality of England and Wales is 3.3 per cent., and of the Russian Empire, 22.3 per cent. For the past forty years that of former New York is 12.2 per cent., Brooklyn, 11 per cent.; Boston, 7.2 per cent.; and Christiania, 9 per cent.; Norway as a whole, 7.9 per cent.

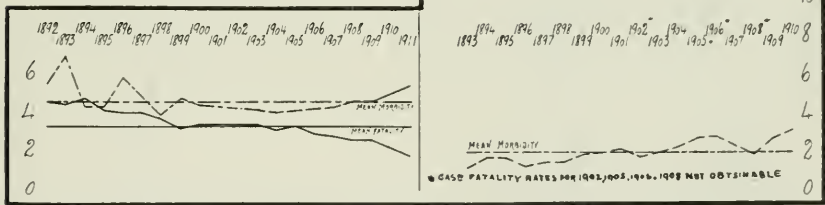


Fig. 12.—Morbidity and case fatality: at the left, in England and Wales, for twenty years, from 1892 to 1911, there being 1,231,018 cases with 41,192 deaths, a case mortality of 3.3 per cent. and a morbidity rate of 4.6 per 1,000 population; at the right, in the Russian Empire, for fourteen years, from 1893 to 1910, there being 3,793,453 cases with 845,641 deaths, a case fatality of 22.3 per cent. and a morbidity rate of 2 per 1,000 population.

Not only is scarlet fever, therefore, more abundant in some places than others, but its fatality in some places is much greater than in others (Table 4). The disease therefore does possess a genius of locality (genius loci).

Periodicity of Occurrence of Scarlet Fever Epidemics.—In all of the places studied scarlet fever is endemic, cases of the disease being

TABLE 5.—CASE FATALITY BY MONTHS AND SEASONS; THE PERCENTAGE OF THE—

Place	Time	No. of Years	Cases, Deaths, % Fatality	January		February		March		April		May
				Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality
Providence.....	{ 1885 to 1913	29	15,597 1,084 7%	C 1,924 D 129 6.7%	12.3 11.9	1,520 123 8.1%	9.7 11.3	1,646 116 7%	10.6 10.7	1,656 118 7.1%	10.6 10.9	1,310 96 7.3%
St. Louis..... (14,052)	{ 1900 to 1911	11	14,099 853 6.1%	C 1,589 D 76 4.8%	11.3 8.9	1,389 91 6.6%	9.9 10.7	1,724 87 5.0%	12.3 10.2	1,667 94 5.6%	11.9 11.0	1,652 115 7.0%
Washington.....	{ 1892 to 1913	22	9,476 238 2.5%	C 1,397 D 28 3%	14.7 11.8	1,023 31 3%	10.8 13.0	1,029 33 3.2%	10.9 13.9	779 26 3.3%	8.2 10.9	763 27 3.5%
Montreal.....	{ 1905 to 1913	9	7,820 684 8.7%	C 728 D 60 8.2%	9.3 8.8	711 66 9.3%	9.1 9.6	920 94 10.2%	11.8 13.7	830 85 10.2%	10.6 12.4	791 84 10.6%
Nuremberg.....	{ 1890 to 1912	23	18,654 993 5.3%	C 1,659 D 83 5.0%	8.9 8.4	1,538 91 5.9%	8.2 9.2	1,595 90 5.6%	8.6 9.1	1,469 76 5.2%	7.9 7.7	1,463 69 4.7%
Japan.....	{ 1897 to 1912	16	8,882 1,452 16.3%	C 695 D 113 16.3%	7.8 7.8	773 135 17.5%	8.7 9.3	1,039 152 14.6%	11.7 10.5	1,042 152 14.6%	11.7 10.5	934 128 13.7%
Total cases (74,481) Total deaths..... Case fatalities, %...	74,528 5,304 7.1%	C 7,992 D 489 6.1%	9.2	6,954 537 7.7%	10.1	7,953 572 7.2%	10.8	7,443 551 7.4%	10.4	6,913 519 7.5%
Philadelphia.....	{ 1908 to 1912	5	11,965 741 6.2%	C 1,092	9.1	1,043	8.7	1,296	10.8	1,332	11.1	1,339
Paris (75,456).....	{ 1896 to 1910	15	72,189 2,142 3%	C 5,395	7.1	5,847	7.7	7,281	9.6	7,939	10.5	9,750
Norway (232,797).....	{ 1867 to 1910	43	233,587 18,566 7.9%	27,298	11.7	22,221	9.5	20,881	9.0	17,453	7.5	17,670
Grand total cases... (394,669) Grand total deaths...	392,269 26,743 6.8%	C 41,777	10.6	36,065	9.1	37,411	9.1	34,167	8.7	35,672
England and Wales...	{ 1892 to 1900	9	January-February-March Cases Deaths Fatality, % 112,627 5,225 4.6						April-May- Cases 118,467		

—CASES OCCURRING IN EACH MONTH; THE PERCENTAGE OF DEATHS IN EACH MONTH

May	June		July		August		September		October		November		December	
Mo.'s % of Year's Total	Cases, Deaths, % Fatal- ity	Mo.'s % of Year's Total	Cases, Deaths, % Fatal- ity	Mo.'s % of Year's Total	Cases, Deaths, % Fatal- ity	Mo.'s % of Year's Total	Cases, Deaths, % Fatal- ity	Mo.'s % of Year's Total	Cases, Deaths, % Fatal- ity	Mo.'s % of Year's Total	Cases, Deaths, % Fatal- ity	Mo.'s % of Year's Total	Cases, Deaths, % Fatal- ity	Mo.'s % of Year's Total
8.4	996 63	6.4	646 49	4.1	661 54	4.2	846 57	5.4	1,318 89	8.5	1,442 87	9.2	1,632 103	10.5
8.9	6.3%	5.8	7.6%	4.5	8.2%	5.0	6.7%	5.3	6.8%	8.2	6.0%	8.2	6.3%	9.5
11.8	1,107 91	7.9	524 44	3.7	409 41	2.9	577 32	4.1	808 46	5.8	1,189 57	8.5	1,417 79	10.1
13.4	8.2%	10.7	8.4%	5.2	10.0%	4.8	5.5%	3.8	5.7%	5.4	4.8%	6.7	5.6%	9.3
8.1	530 16	5.6	333 8	3.5	422 11	4.5	418 4	4.4	748 17	7.9	903 15	9.5	1,131 22	11.9
11.3	3%	6.7	2.4%	3.4	2.6%	4.6	1%	1.7	2.3%	7.1	1.7%	6.3	1.9%	9.2
10.1	618 43	7.9	400 30	5.1	372 35	4.8	451 28	5.8	564 46	7.2	626 55	8.0	809 58	10.3
12.3	7%	6.3	7.5%	4.4	9.4%	5.1	6.2%	4.1	8.2%	6.7	8.8%	8.0	7.2%	8.5
7.8	1,463 88	7.8	1,380 81	7.4	1,209 86	6.5	1,413 72	7.6	1,931 78	10.4	1,870 94	10.0	1,664 85	8.9
7.7	6.0%	8.9	5.9%	8.2	7.1%	8.7	5.1%	7.3	4.0%	7.9	5.0%	9.5	5.1%	8.6
10.5	825 151	9.3	677 131	7.6	378 70	4.3	318 61	3.6	561 84	9.3	771 114	8.7	869 161	9.8
8.8	18.3%	10.4	19.4%	9.0	18.5%	4.8	19.2%	4.2	15.0%	5.8	14.8%	7.9	18.5%	11.1
9.8	5,539 452	8.2%	3,960 343	8.7%	3,451 297	8.6%	4,023 254	6.3%	5,930 360	6.1%	6,801 422	6.2%	7,522 508	9.6
11.2	1,029	8.6	514	4.3	429	3.6	497	4.2	870	7.3	1,105	9.2	1,419	11.9
12.9	9,777	13.0	8,698	11.5	4,540	6.0	2,917	3.9	3,830	5.1	4,395	5.8	5,087	6.7
7.6	17,391	7.5	14,711	6.3	13,772	5.9	14,443	6.2	19,426	8.3	23,831	10.2	23,700	10.2
9.0	33,736	8.5	27,883	7.1	22,192	5.6	21,880	5.5	30,056	7.6	36,132	9.2	37,728	6.0
June Deaths 5,090			July-August-September Deaths 5,440						October-November-December Deaths 6,754					
Fatality, % 4.3			Fatality, % 3.6						Fatality, % 3.7					
Cases 149,730									Cases 176,793					

practically always present; the fluctuations in the amount, as shown by the annual morbidity rates, follow no rule as regards periodicity, in contrast to what one sees stated by some authors (Figs. 1 to 12). The prevalence of the disease may be increased for a single year, the previous and succeeding years being below the average, but it is more

common to see two, three, and less often four or even five years in succession, in which the amount of scarlet fever is increased. In other words, an epidemic either subsides slowly during two or three or more years, or may attain a greater height in its second than in its first year. It goes slowly or comes slowly, as compared to measles, for instance, in which an epidemic attains its height very quickly and subsides equally so. There may be but a single year between epidemics of scarlet fever, or there may be two, three, four, five or more years between them, with low morbidity rates during the interim. A standard for judging the prevalence of scarlet fever in a community at any given time is found only in the mean morbidity rate of the community in question.

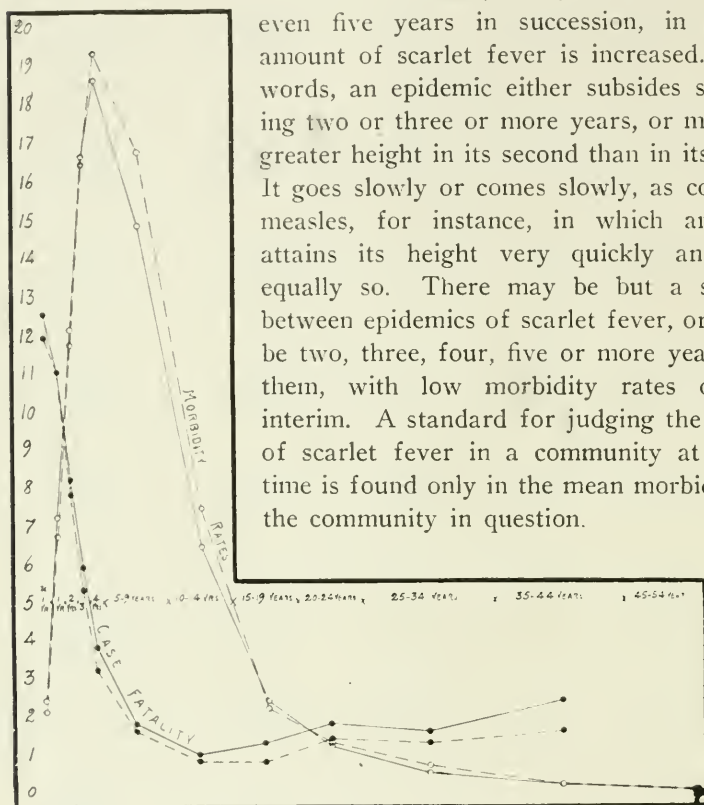


Fig. 13.—Graphic representation of the last two double columns in Table 7. Figures 14, 15, 16, 17 and 18 are made in the same way as 13, except where figures for the sexes were not to be had. Morbidity and case fatality, as influenced by age and sex, in London, for nineteen years, from 1894 to 1912, there being 159,077 cases among males, with 5,206 deaths, a case fatality of 3.3 per cent. and a morbidity rate of 3.96 per 1,000 population; 176,349 cases among females, with 4,817 deaths, a case fatality of 2.7 per cent. and a morbidity rate of 3.92 per 1,000 population. The solid lines represent the data for males; the broken lines for females.

Decrease of Incidence.—There has been no striking reduction in the annual morbidity rates anywhere during the periods studied (Table 3 and Figs. 1 to 12). They fluctuate from year to year within essentially the same limits now as years ago. The smaller the place, the greater are the annual fluctuations in morbidity rates.

This is seen particularly in Christiania (Fig. 10), the smallest place studied. On the other hand, where the annual rates for the whole of England and Wales (Fig. 12) are compared, the localities included are so numerous and different that there is a consolidation of local differences, so that the rates for the whole country fluctuate from year to year within comparatively narrow limits. Norway (Fig. 11) shows a decided tendency to a decline in the prevalence of scarlet fever and the same is true of Philadelphia (Fig. 6). The Russian Empire (Fig. 12) and Montreal (Fig. 8) show tendencies in the opposite direction, namely toward an increase in morbidity rates.

Decrease of Fatality.—The most striking fact about the case fatality of scarlet fever in the past half century has been its consistent, general, and marked reduction (Table 4 and Figs. 1 to 12). This diminution in case fatality has occurred in the absence of specific treatment, and while there have been frequent irregularities in its descent, the general downward course is unmistakable and considerable, even comparable to diphtheria in its fall in some places. This reduction exceeds that of the general reduction in infant mortality. In the comparison of localities, therefore, simultaneous periods must be considered. In Christiania in

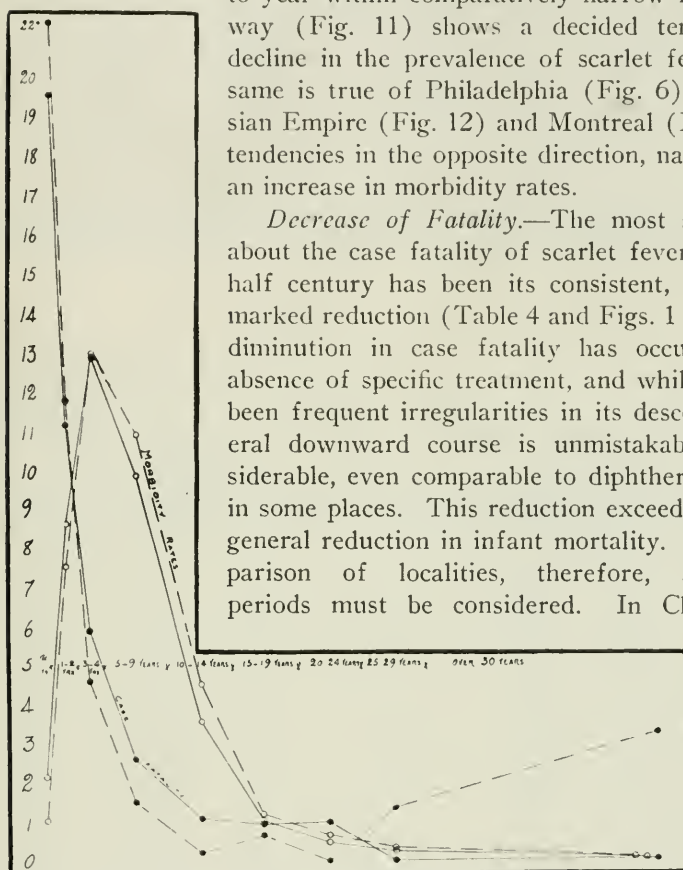


Fig. 14.—Morbidity and case fatality, as influenced by age and sex, in Christiania, for twenty-one years, from 1890 to 1910, there being 5,656 cases among males, with 271 deaths, a case fatality of 4.8 per cent. and a morbidity rate of 2.83 per 1,000 population; 6,122 cases among females, with 210 deaths, a case fatality of 3.43 per cent. and a morbidity rate of 2.51 per 1,000 population. The solid lines represent the data for males; the broken lines for females.

the past five years the case fatality ranged from 1 to 2.8 per cent.; between forty and fifty years ago it varied from 8 to 30 per cent. In Norway, as a whole, it has lately been in the neighborhood of 2 per cent.; forty to fifty years ago it was from 12 to 15 per cent. In former New York and Brooklyn it has lately been in the vicinity of

TABLE 6.—COMPARISON OF SEXES IN POPULATION—

Place and Time	Number of Years	Total of Annual Populations	Populations	
			Males	Females
Nuremberg (1890 to 1912).....	21	5,282,848	2,606,486	2,676,362
London (1894 to 1912).....	19	85,186,789	40,171,943	45,014,846
Norway (1880 to 1910).....	30	65,302,907	31,517,229	33,785,678
Totals.....		155,772,544	74,295,658	81,476,886

* This table shows morbidity rates by sex to be almost identical; and the sexes in practically the same proportion among the population and the cases. Case fatality is higher among males.

† The cases among males were 47.82 per cent. of the whole number of cases; those among females, 52.18 per cent.

TABLE 7.—DISTRIBUTION OF MORBIDITY AND—
(LONDON, 1894-1912—

Age, Years	Population		Population in Percentage		Cases of Scarlet Fever	
	Males	Females	Males	Females	Males	Females
Under 1.....	992,009	988,546	50.08	49.92	2,376	2,035
1.....	899,969	896,932	50.08	49.92	6,509	6,045
2.....	947,475	941,368	50.16	49.84	11,467	11,003
3.....	925,265	936,942	49.68	50.32	15,326	15,354
4.....	903,504	902,521	50.02	49.98	16,794	17,373
5 to 9.....	4,268,466	4,301,869	49.80	50.20	63,150	71,939
10 to 14.....	3,918,305	3,989,812	49.54	50.46	25,085	29,665
15 to 19.....	3,782,466	4,170,392	47.56	52.44	9,015	9,119
20 to 24.....	3,730,462	4,579,650	44.89	55.11	4,490	6,156
25 to 34.....	6,815,812	7,989,570	46.03	53.97	3,638	5,846
35 to 44.....	5,322,498	5,977,617	47.10	52.90	910	1,359
45 to 54.....	3,826,089	4,304,297	47.05	52.95	237	322
55 and over.....	3,839,623	5,035,330	43.26	56.74	80	133
Totals.....	40,171,943	45,014,846	47.20	52.80	159,077	176,349
Grand total.....	85,186,789		335,426	

* This table (in part represented graphically in Figure 13) shows in the last two double columns case fatality and morbidity rates with distinction of sex and age. For example, at the age of 4 years, the case fatality among boys was 3.8 per cent. and 3.2 per cent among girls. Out of each 1,000 living boys

—AND AMONG SCARLET FEVER CASES AND DEATHS*

Population, per Cent.		Morbidity Rate per 1,000		Scarlet Fever Cases†		Deaths from Scarlet Fever‡		Case Fatality, per Cent.	
Male	Female	Male	Female	Males	Females	Males	Females	Males	Females
49.3	50.7	3.19	3.55	8,324	9,497	502	475	6.03	5.0
47.2	52.8	3.96	3.92	159,077	176,349	5,206	4,817	3.27	2.73
48.3	51.7	2.49	2.43	78,263	82,203	5,344	4,545	6.83	5.53
47.7	52.3	3.31	3.29	245,664	268,049	11,052	9,837	4.50	3.67

‡ The deaths among males were 53 per cent. of the whole number of deaths; those among females, 47 per cent.

—CASE FATALITY ACCORDING TO SEX AND AGE
—NINETEEN YEARS)*

Cases in Percentage		Deaths from Scarlet Fever		Deaths in Percentage		Percentage of Case Fatality		Morbidity Rates per 1,000	
Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
53.87	46.13	297	242	55.10	44.90	12.5	11.9	2.4	2.1
51.85	48.15	717	662	51.99	48.01	11.0	11.0	7.2	6.7
51.03	48.97	944	856	52.44	47.56	8.2	7.8	12.1	11.7
49.95	50.05	907	815	52.67	47.33	5.9	5.3	16.6	16.4
49.15	50.85	632	556	53.20	46.80	3.8	3.2	18.6	19.3
46.75	53.25	1,162	1,172	49.79	50.21	1.8	1.6	14.8	16.7
45.82	54.18	256	241	51.51	48.49	1.0	0.8	6.4	7.4
49.71	50.29	114	75	60.32	39.68	1.3	0.8	2.4	2.2
42.18	57.82	81	86	48.50	51.50	1.8	1.4	1.2	1.3
38.36	61.64	59	77	43.38	56.62	1.6	1.3	0.5	0.7
40.11	59.89	22	21	51.16	48.84	2.4	1.6	0.2	0.2
42.40	57.60	12	9	57.14	42.86	5.1	2.8	0.06	0.07
37.56	62.44	3	5	37.50	62.50	3.8	3.8	0.02	0.02
.....	5,206	4,817	3.3	2.7	3.96	3.92
.....	10,023							

at the age of 4 years 18.6 had scarlet fever. Similarly, 19.3 out of each 1,000 living girls of 4 years had scarlet fever. Absolute figures and ratios of the sexes in the population, the reported cases and deaths for scarlet fever, at various ages, are presented.

5 per cent., compared to from 20 to 35 per cent. forty years ago. In Nuremberg the recent fatality is in the neighborhood of 3 per cent., while twenty years ago 7 to 15 per cent. was more common.

In contrast to the rule of diminishing case fatality, attention must be called to the fact that in the Russian Empire (Fig. 12) the later case fatality has been in the neighborhood of 30 per cent., while twenty years ago it was only half this amount. Japan (Fig. 7) likewise has a case fatality which has a decided tendency toward increase. As yet the amount of scarlet fever in Japan according to its health reports is exceedingly small.

In Australia and New Zealand there have been very low morbidity rates and case fatality (1.5 per cent.).

Explanation of Lowered Fatality.—Heubner says:

Sydenham in the year 1664 looked upon scarlet fever as possessing no great importance, about as we today regard German measles, and fifteen years later it appeared in the practice of this great clinician in London with a formidability which was scarcely inferior to plague. A century and a half later a physician of equal rank, Bretonneau, stated that a scarlet fever patient died only when he was wrongly treated, but was obliged a few years later to confess how greatly he had erred when he found himself in the midst of an epidemic with a shocking mortality.

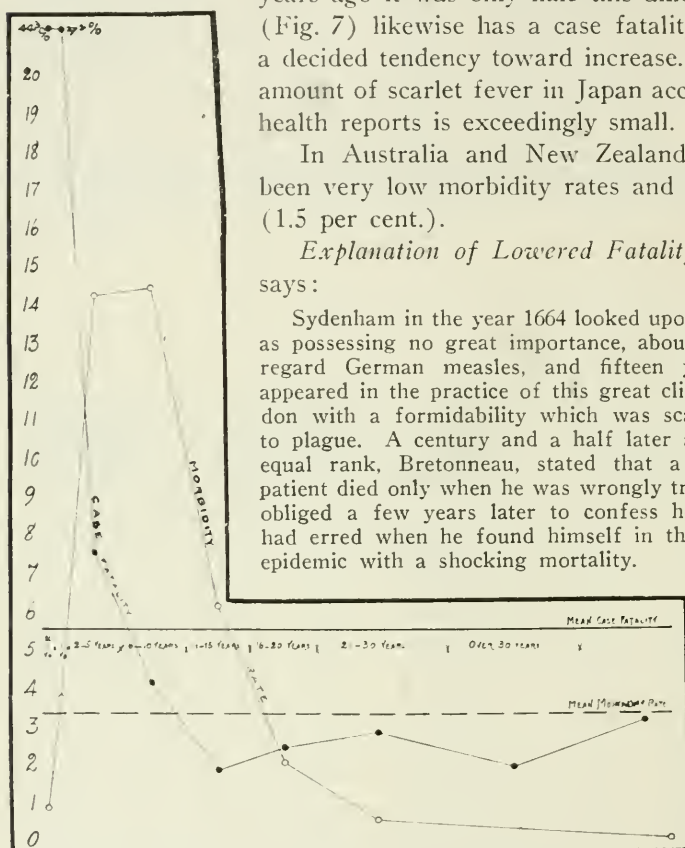


Fig. 15.—Morbidity and case fatality as influenced by age, in Nuremberg. for twenty-three years, from 1890 to 1912, there being 17,835 cases with 977 deaths, a case fatality of 5.5 per cent. and a morbidity rate of 3.32 per 1,000 population.

In the reports of the Local Government Board, London, for 1909-1910, the medical officer said: "There can be no doubt in the minds of those who knew scarlet fever as it existed thirty or forty years ago that it is at present a much milder disease."

There is certainly evidence to favor the opinion that the disease is milder today than formerly.

The removal of scarlet fever patients to contagious hospitals has improved the care of many patients and may be a contributing factor to lowered fatality. Over 90 per cent. of the patients in London are treated in contagious hospitals, whereas in 1890 there were but 42.8 per cent. thus treated. As patients in hospitals are usually given diphtheria antitoxin, it is quite probable that this is another important factor, because combined scarlet fever and diphtheria have had a high fatality.

It is conceivable, but incapable of proof, that there is an immunity which may have been increasing in the 300 years more or less since the disease was first recognized.

Variation of Virulence of Epidemics.—In recent monographs may be found statements that morbidity and case fatality run essentially parallel. A comparison of the morbidity and fatality curves on very carefully prepared charts (Figs. 1 to 12) shows as a matter of fact that they are not in the least parallel. Both skip about most irregularly. A

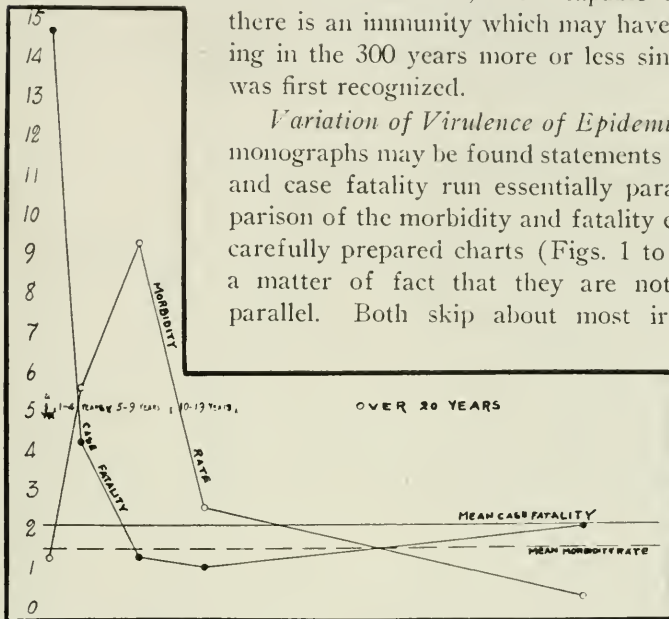


Fig. 16.—Morbidity and case fatality, as influenced by age, in Washington, D. C., for six years, from 1908 to 1913, there being 3,320 cases with 68 deaths, a case fatality of 2.1 per cent. and a morbidity rate of 1.5 per 1,000 population.

large epidemic may have a low case fatality, or it may have a high case fatality which diminishes as the epidemic increases. On the other hand, a small incidence of scarlet fever may be attended with a high case fatality, while at another time in the same place a like morbidity may be attended by a low case fatality. Grouping the figures from various localities obscures local differences in morbidity and fatality and conceals striking variations in them.

Influence of Season.—The height of an epidemic of scarlet fever may occur at any season of the year (Table 5). January and December usually have the maximum number of cases, and August and September the smallest number. In Paris the maximum number is quite

TABLE 8.—SCARLET FEVER AS INFLUENCED BY SCHOOL (LONDON)*

Year	Cases in Last Four Weeks of School			Cases in Vacation Four Weeks (August)				Cases in First Four Weeks of School			
	0 to 3 Years	3 to 13 Years	Over 13 Years	0 to 3 Years	Change, %	3 to 13 Years	Change, %	Over 13 Years	Change, %	3 to 13 Years	Change, %
1911	110	650	98	80	-27.3	460	-29.2	111	+13.3	836	+81.7
1910	94	609	114	87	-7.4	499	-18.1	92	-19.3	624	+25.1
1909	187	1,100	215	148	-20.9	812	-26.2	169	-21.4	1,238	+52.5
1908	161	1,206	230	169	+5.0	1,075	-10.9	214	-7.0	1,537	+43.0
1907	270	1,540	316	259	-4.1	1,429	-7.2	304	-3.8	2,065	+44.5
1906	184	1,330	233	195	+6	947	-28.8	208	-10.7	1,471	+55.3
1905	186	1,063	186	208	+11.8	1,160	+6.1	189	+1.6	1,647	+42
1904	136	839	139	98	-22.2	638	-24	141	+3.6	967	+51.6
1903	123	810	137	163	+32.5	612	-24.4	127	-19.1	789	+28.9
1902	186	1,143	257	203	+9.1	889	-22.7	270	+5.1	1,086	+22.9
1901	184	1,141	352	169	-8.2	890	-22	281	-20.2	1,391	+56.3
1900	108	607	202	90	-16.7	512	-15.7	182	-9.9	895	+68.9
1899	175	1,051	246	141	-19.4	793	-24.5	238	-3.3	1,220	+53.8
1898	176	997	197	137	-22.2	680	-31.8	163	-17.3	907	+33.4
1897	260	1,416	335	223	-10.4	1,240	-12.4	318	-5.1	1,803	+45.4
1896	275	1,681	420	348	+26.5	1,632	-2.9	446	+18.1	1,850	+21.3
1895	254	1,390	312	252	+7.7	1,084	-22	254	-18.6	1,518	+40
1894	204	1,026	220	189	-7.4	808	-21.2	181	-17.7	1,079	+33.5
Totals	3,243	19,629	4,929	3,169	-2.28	16,160	-17.67	3,941	-6.81	23,053	+42.65
											+19.0

* This table shows the cases of scarlet fever reported in London, 1894 to 1911, for the last four weeks of school, during the four weeks vacation in August, and the first four weeks after schools opened. The greatest change took place in children of school age, 3 to 13 years. The percentages of fall and increase in case reports are shown.

constantly in the early summer. Case fatality is highest in the summer months, lowest in the fall.

Susceptibility of Sexes.—Quite a difference is to be found in the absolute numbers of cases in the two sexes, the higher number representing the females. The reason for this is made clear if we consider the composition of the general population, where it is found that the

total number of females is considerably greater than the total number of males. The writer has calculated the number of cases of scarlet fever per 1,000 males in the population, and the same for females and found that the morbidity rates thus obtained for the two sexes are almost identical. The number of cases of scarlet fever among males bears almost the same ratio to the number of cases among females as the number of males bears to the number of females in the entire population (Table 6). The slight difference which exists, however, shows a slightly increased susceptibility among males. Roughly, however, we may say that the sexes as a whole show about equal susceptibility. During the first four years of life boys are more susceptible to the disease, while between 5 and 15 years girls are distinctly more susceptible (Table 7 and Figs. 13, 14,

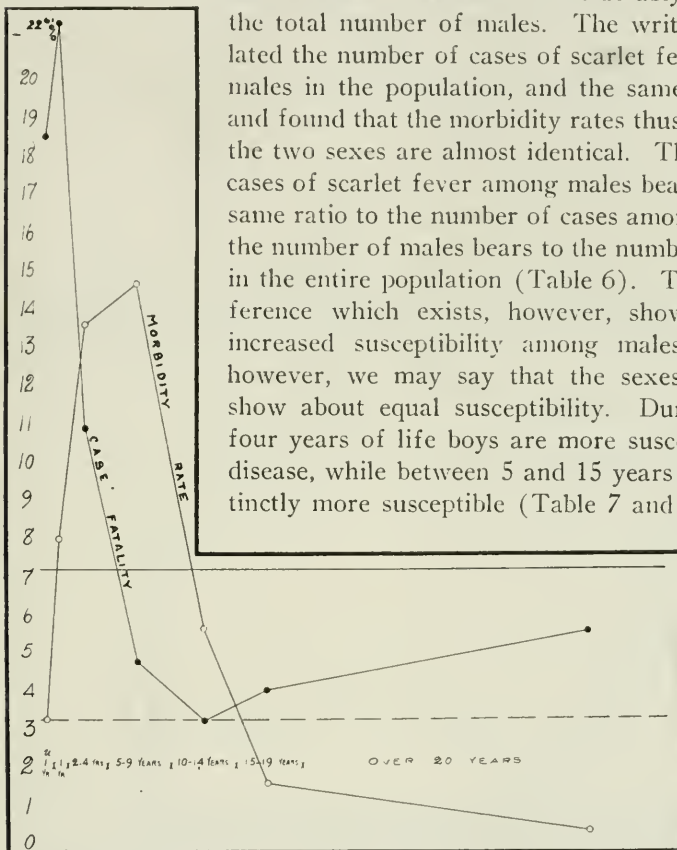


Fig. 17.—Morbidity and case fatality, as influenced by age, in Providence, for twenty-seven years, from 1887 to 1913, there being 14,278 cases with 1,017 deaths, a case fatality of 7.12 per cent. and a morbidity rate of 3.2 per 1,000 population.

21, 22 and 23). Otherwise sex has little or no influence on susceptibility.

Nichols³ has shown by means of a stupendous compilation of birth statistics that about 1,056 boys are born to each 1,000 girls. The pre-

3. Nichols, J. B.: The Numerical Proportions of the Sexes at Birth, Am. Anthropol. Assn., Memoirs, Lancaster, Pa., 1907, i. Part 4.

ponderance of boys over girls in the population keeps up until about the age of 20 years, and thereafter women predominate. This only accentuates the peculiar sex preference of scarlet fever just mentioned, namely, greater the first 4 years among boys; greater among girls from 5 to 15 years.

Sex as Influencing Fatality.—The number of deaths from scarlet fever is both absolutely and relatively greater in boys than in girls, the deaths among boys ranging from 50.5 to 53.7 per cent. of the total deaths. Among 513,713 cases, there occurred 20,889 deaths, of which 53 per cent. were among boys and 47 per cent. among girls. The case fatality among boys was 4.5 per cent., as against 3.67 per cent. among girls, and in each of the localities case fatality was higher among boys. For Norway case fatality among boys was 6.83 per cent. against 5.53 per cent. for girls; in London 3.27 per cent. against 2.73 per cent., and in Nuremberg 6.03 per cent. against 5 per cent. It is thus seen that case fatality is 20 per cent. greater among boys than among girls. Furthermore, it is consistently higher for males at

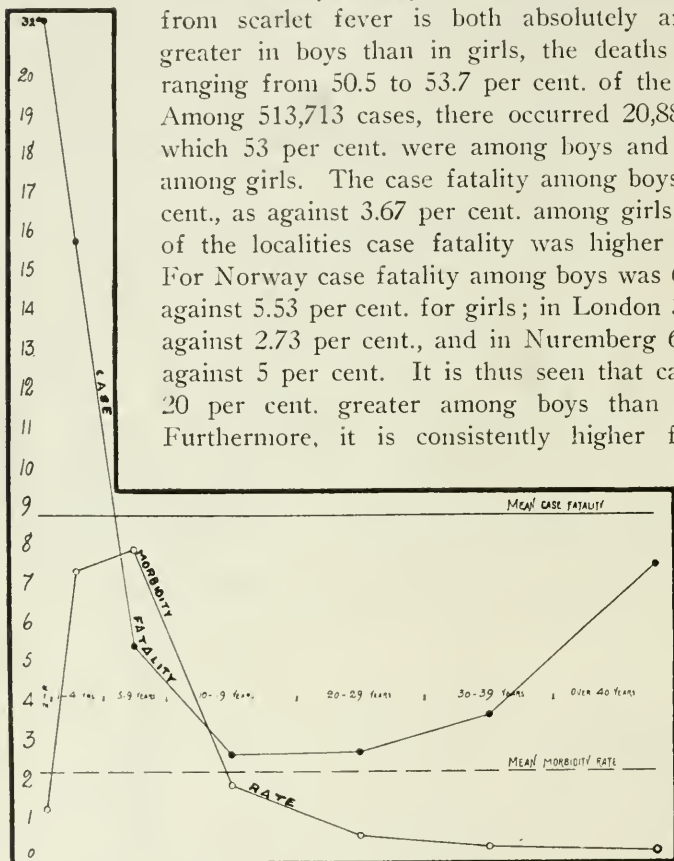


Fig. 18.—Morbidity and case fatality, as influenced by age, in Montreal, for nine years, from 1905 to 1913, there being 7,820 cases with 684 deaths, a case fatality of 8.7 per cent. and a morbidity rate of 2.1 per 1,000 population.

each age period throughout life (case fatality curves, Figs. 13 and 14).

Age of Greatest Susceptibility.—Nearly half of all cases of scarlet fever occur in children at the ages 3, 4, 5, 6 and 7 years, and are quite evenly distributed at about 10 per cent. in each of these years (Fig. 19). Board of Health figures show somewhat over 1 per cent. of cases

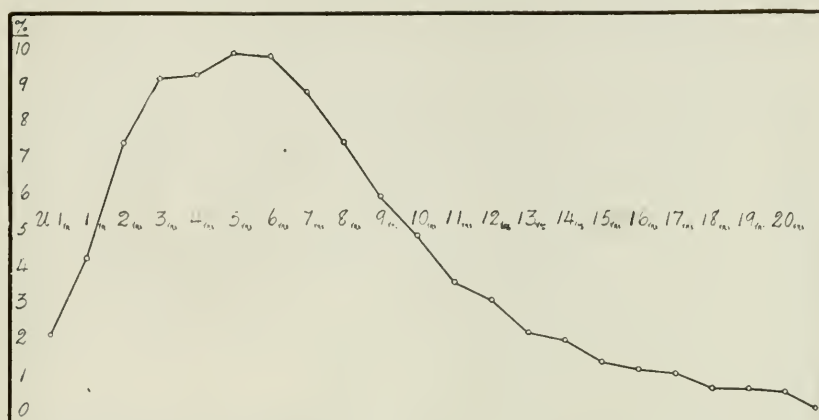


Fig. 19.—Age distribution of scarlet fever in the years up to 20, expressed for each year in percentage of the total, in Providence, for twenty-seven years, from 1887 to 1913, there being 14,278 cases.

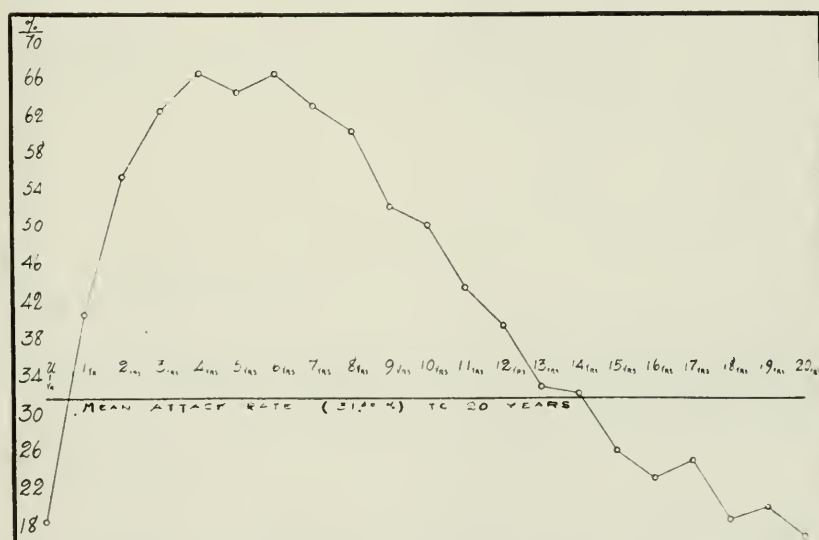


Fig. 20.—Age susceptibility to scarlet fever, in Providence, for twenty-seven years, from 1887 to 1913, based on 45,388 persons, not previously having had the disease, exposed in their own homes; there were 14,278 cases resulting, or an average of 31.5 per cent. for all ages up to 20 years.

occurring in children under 1 year of age,⁴ the incidence rising rapidly to age 3, where it remains level for five years, falling by age 15 to about 1 per cent.

At the ages 3, 4, 5, 6 and 7 years, about two children out of three contract scarlet fever if exposed to it in their homes (Fig. 20).

Scarlet fever seems more peculiarly a disease of childhood than measles or whooping cough, although most children have the latter and acquire a consequent immunity. Nonimmune adults quite readily fall ill with them when exposed, but not so with scarlet fever, with which few exposed adults become affected. About 90 per cent. of cases occur in children under 15 years of age.

Age of Greatest Fatality.—The number of deaths per 100 cases is high during infancy, about 12 to 20 per cent., but rapidly diminishes with each succeeding year of life until between 10 and 14 years, when it is lowest, being in the neighborhood of 1 per cent. From this age

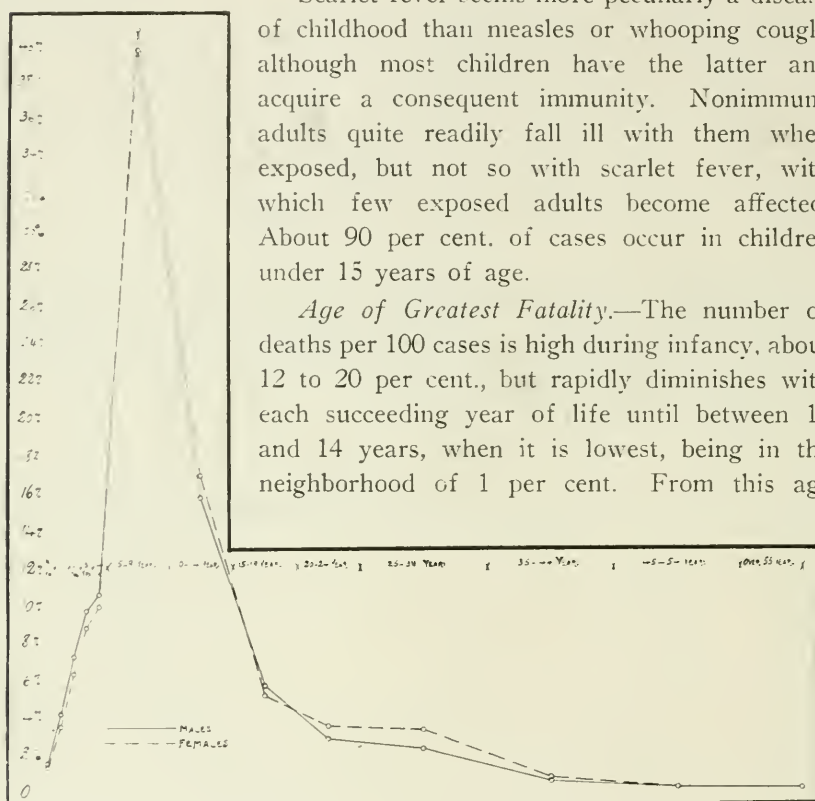


Fig. 21.—Distribution of cases in percentage of the total for each sex at the various ages of life, in London, for nineteen years, from 1894 to 1912, there being a total of 335,426 cases, 159,077 among males, or 47.43 per cent., and 176,349 among females, or 52.57 per cent. of the total.

on the disease has a slowly increasing death rate (case fatality curves, Figs. 13 to 18).

About 90 per cent. of deaths occur in children under 10 years of age.

4. A proportion of 1 + per cent. for cases of scarlet fever in children under 1 year of age is regarded by clinicians of wide experience as very high, and they properly raise the question of accuracy of diagnosis in young babies reported as having the disease.

CONCLUSIONS

Figures obtained from board of health notifications of cases and deaths for scarlet fever, support the following conclusions:

Periodicity in the appearance of epidemics of scarlet fever cannot be made out.

Morbidity and mortality rates for scarlet fever seem independent of each other.

A decline in morbidity has not generally been made out. (Notification is at present probably more thorough than ever before. While insusceptible of proof, it is probable that this factor has served to keep morbidity rates in most places approximately level.)

Where notification has been of longest duration and most thorough (Norway) a reduction in the incidence of scarlet fever has been observed.

Season itself does not influence morbidity.

The sexes as a whole show equal susceptibility. Under 5 years of age boys are more susceptible, while between 5 and 15 years of age girls are more susceptible than boys.

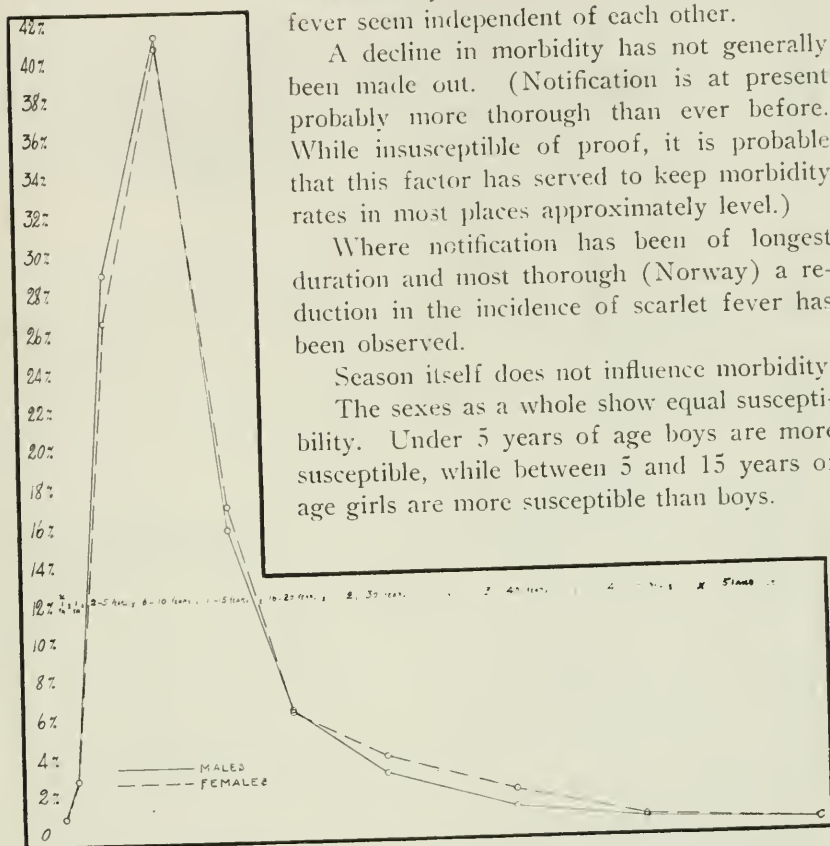


Fig. 22.—Distribution of cases in percentage of the total for each sex at the various ages of life, in Nuremberg, for twenty-one years, from 1890 to 1910, there being a total of 17,821 cases, 8,324 among males, or 46.71 per cent., and 9,497 among females, or 53.29 per cent. of the total.

About half of the cases occur in children between 3 and 8 years, and 90 per cent. in those under 15 years of age.

About two children out of three between 3 and 8 years of age contract scarlet fever if exposed to it in their homes, if they have not previously had it.

Scarlet fever appears to be a milder disease than formerly.

Different epidemics may vary greatly in virulence.

Scarlet fever has been regularly more prevalent in some places than in others.

It has been consistently attended by greater fatality in some places than in others.

At all ages males succumb more readily to it than females.

Case fatality is lowest in those about 10 to 15 years of age. The younger the child, the less is his chance of recovery.

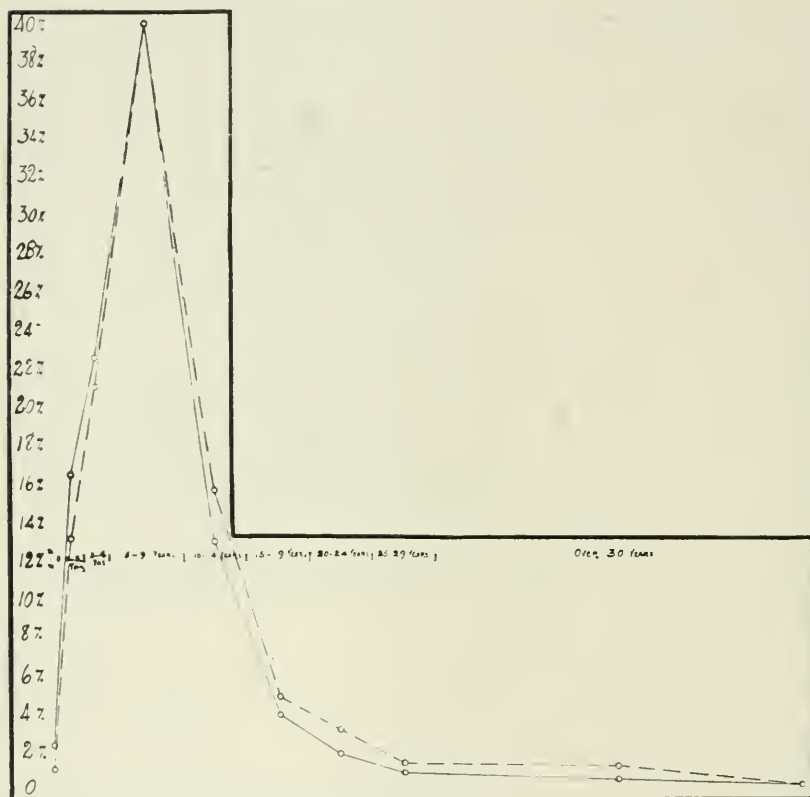


Fig. 23.—Distribution of cases in percentage of the total for each sex at various ages, in Christiania, for twenty-one years, from 1890 to 1910, there being a total of 11,778 cases, 5,656 among males, or 48.02 per cent., and 6,122 among females, or 51.98 per cent. of the total. The solid line indicates the data for males; the broken line, for females.

About 90 per cent. of deaths from scarlet fever occur in those under 10 years of age.

Officials of the Library of the Surgeon-General's Office, Mr. Starkey in particular, have generously rendered much aid in procuring health reports from various parts of the world, from which the figures were obtained. Dr. Frederick S. Crum, assistant statistician of the Prudential Insurance Company, gave valuable assistance in obtaining statistics of populations with distinction of sex and age.

1612 I Street.

CONGENITAL DEXTROCARDIA WITH PATENT DUCTUS OVALE

NECROPSY AT NINE MONTHS *

H. J. MORGAN, M.D.

TOLEDO, OHIO

In view of the rarity of congenital dextrocardia alone, as shown by the review of the literature recently published by Moffett and Neu-hoff,¹ this case is reported. As in almost all cases reported this patient suffered from congenital defect of the heart itself. Its occurrence in a girl and the opportunity for necropsy are interesting features.

CASE REPORT

Jean M., a girl, aged about 1 month, was brought to the Maternity and Children's Hospital for adoption, August 18, 1915.

On physical examination the baby was found to weigh 5 pounds 5 ounces and its length of body to be $18\frac{3}{4}$ inches, circumference of head $13\frac{3}{4}$ inches, of chest $11\frac{1}{2}$ inches. The temperature was 99, pulse 144, respiration 40.

The skin of the whole body was cyanotic, more marked over the face and hands. The respiration was rapid, with a sinking in of the suprasternal notch and epigastrium on inspiration, and an active movement of alae nasi. The conjunctivae were congested, but otherwise the eyes, ears, nose and throat were normal.

The respiration was wheezing and difficult, and most râles were perceptible over both lungs in front and at the back, but no other abnormalities of the lungs were present.

The apex of the heart was felt on the right side 6 cm. to the right of the midsternal line at the fourth interspace; the right border at the fifth interspace was $5\frac{1}{2}$ cm., at the fourth interspace 6 cm., at the third interspace $5\frac{1}{2}$ cm. to the right of the midsternal line; the left border was 1 cm. to the left of the midsternal line at the fourth interspace, and the upper border was at the second interspace on the right side. At the first examination a distinct, rough, systolic murmur was heard, loudest at the apex, but more or less distinct over the whole cardiac area. It was not transmitted, and no thrill was felt.

Above the heart in the second interspace an area of dullness extending 3 cm. to the left of the midsternal line was felt. This was taken to be the enlarged thymus.

The liver and spleen seemed to be in normal position. No bony changes and no clubbing of the fingers were present, and no other abnormalities could be detected. A roentgenogram taken at this time (Fig. 1) shows the correctness of the foregoing findings.

Blood examination showed hemoglobin 130 per cent. (Sahli), red cells 6,250,000, white cells 9,200, polymorphonuclears 47.5 per cent., large leukocytes 20 per cent., small leukocytes 32.5 per cent., with no abnormal red cells.

The thymic enlargement and the wheezing, bubbling character of the respiration suggested the possibility of thymic asthma, and so the baby was treated by Roentgen-ray exposures, as outlined in a report of cases of this disorder successfully treated by us,² but no benefit followed.

Except for a gain of 4 pounds 14 ounces in the next eight and one-half months no marked changes occurred in her condition. While her color was

* Submitted for publication May 22, 1916.

1. Moffett and Neuhoﬀ: *AM. JOUR. DIS. CHILD.*, 1915, x, 1.

2. Morgan and Dachtler: *Surg., Gynec. and Obst.*, 1914, xix, 781.

at times fairly good, she usually showed slight cyanosis of the face and hands, and when exposed to cold or lifted about, she became very deeply cyanosed.

The heart murmur heard at first examination was not heard again for about a month. It never became constant, and when heard it was never transmitted to the neck and no thrill was ever felt.

Death occurred May 2, 1916, when the girl was about 9 months of age, following two severe convulsions.

Necropsy.—When the chest was opened it was seen that the left lobe of the thymus was quite large, the tip being in the fourth interspace, the extreme left edge being $2\frac{1}{2}$ cm. to the left of the midsternal line.

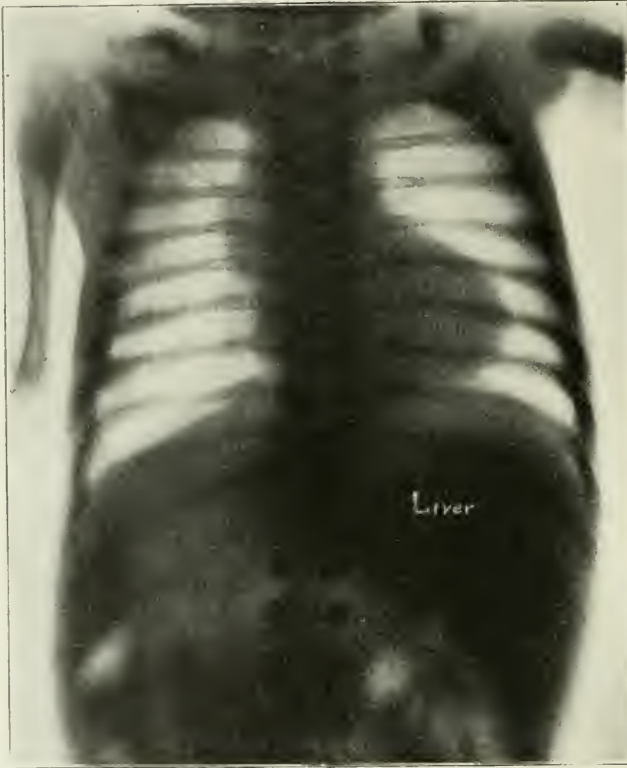


Fig. 1.—Roentgenogram showing dextrocardia.

The heart was on the right side, the lungs, including the lobar divisions, were normal. The liver, stomach and spleen were in normal position and without abnormalities. The pericardium contained 18 c.c. clear fluid. The heart was globular in shape, the walls of the left ventricle very thick, those of the right rather thin, with a muscular defect which showed as a dimple in the external surface, not extending through the wall. The heart valves were normal except for the patent ductus ovale. There was no interventricular defect. The large vessels leading off from the rather exaggerated aortic arch were in normal position.

Thanks are due to H. H. Dachtler for the Roentgen-ray work and to W. E. Mosely for the necropsy.

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PYELITIS OF INFANCY

I. MODE OF INFECTION *

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There have been two antagonistic theories advanced to explain the mode of the infection of the kidney in pyelitis of infancy. One theory maintains that the infection of the kidney takes place by the ascending route, through urethra, bladder and ureters; the other, that the infection comes by means of the blood and lymphatics. Before discussing the relative merits of these two theories certain facts in regard to pyelitis as it occurs in infants need to be noted. The disease is much more common in girl than in boy infants, the proportion being nearly three to one. The organism most frequently causing the disease is the colon bacillus, which is the offender in from 50 to 90 per cent. of cases. The pathology of the condition is well established. In uncomplicated cases the pelvis of the kidney is the only portion of the urinary tract involved, and there the local lesion is simply a low grade inflammation. The ureters and bladder are normal. Many cases show in addition some degenerative changes in the kidney substance, due to extension of the process inward from the pelvis. When the tissues are invaded by pus-forming cocci, there is secondary abscess formation.

With these facts as a basis, those who believe in the ascending route of infection argue that the colon bacillus enters the urethra, ascends against the urinary stream and, causing no lesions in its progress, localizes in the pelvis of the kidney and by its growth there gives rise to disease. This theory gains its greatest support from the large proportion of cases among girls, who, theoretically with a short urethra and of easy contamination with fecal matter, become more readily infected. There is very little experimental work in its support. Bond¹ showed that in the intestine, fallopian tubes and biliary passages solid particles may be carried upward by a current hugging close to the surface, and that in the ureter, when no urine is coming down, this

* Submitted for publication May 18, 1916.

* From the Children's Medical Department, Massachusetts General Hospital.

* Read at the Twenty-Eighth Annual Meeting of the American Pediatric Society, held at Washington, D. C., May 8-10, 1916.

1. Bond: Med. Rec., New York, 1905, lxviii, 246.

passage upward may also occur. Many others² state the opinion that ascending infection may occur in some or all cases, but they have no sure evidence to support the belief.

Directly against the ascending method of infection are the facts that colon bacilli have never been shown to pass up the normal, unobstructed ureter and that the colon and tubercle bacilli have been introduced repeatedly into the bladder and in the presence of a normal mucous membrane are excreted without causing damage of any kind.³ Ascending infection occurs only in the presence of obstruction to the outflow of urine and cannot occur if the sphincter of the ureter is normal.⁴ It seems to me that the ascending theory of kidney infection so far as it applies to the pyelitis of infancy has not been proved and the facts are against it.

The theory of kidney infection by the blood and lymphatics rests upon much surer ground. The work of Thiele and Embleton⁵ seems to show that bacteria may pass to the kidney by the lymphatics alone, appearing first in the fat capsule and being distributed through the kidney also by the lymphatics. If bacteria appear in the urine, that is, if they have passed through the kidney, they must have reached the kidney by the blood stream. This latter procedure is what occurs in pyelitis, so we must have had a blood infection.

The direct lymphatic connection as shown by Franke⁶ between the colon and the right kidney, which is the kidney most frequently affected in unilateral infection, has led some writers⁷ to believe that bacteria pass directly from the intestine to the kidney by these lymph

2. Among these may be cited the following:

Thomas, J.: *Lancet*, London, 1913, ii, 467.

Wright: *Practitioner*, London, 1909, lxxxii, 344.

McCrea: *Practitioner*, 1910, lxxxv, 346.

Wyman: *Boston Med. and Surg. Jour.*, 1914, clxx, 540.

Freeman: *Jour. Am. Med. Assn.*, 1914, lxiii, 1802.

Cunningham: *Jour. Am. Med. Assn.*, 1915, lxiv, 231.

Heubner: *Jahrb. f. Kinderh.*, 1913, lxxvii, 1.

Ross: *Lancet*, London, 1915, i, 654.

Shaw: *Clin. Jour.*, 1908, xxxi, 273.

Box: *Brit. Med. Jour.*, 1910, ii, 1128.

Barnard: *Lancet*, London, 1905, ii, 1243.

Herringham: *Clin. Jour.*, 1909-1910, xxxv, 241.

Sampson: *Bull. Johns Hopkins Hosp.*, 1903, xiv, 334.

3. Leutscher: *Bull. Johns Hopkins Hosp.*, 1911, xxii, 361. Bauereisen: *Ztschr. f. gynäk. Urol.*, 1910, ii, 132.

4. Rovsing: Sixteenth International Medical Congress, Budapest, 1909.

5. Thiele and Embleton: *Proc. Roy. Soc. Med., Path. Sec.*, 1913-1914, vii, 69.

6. Franke: *Mitt. a. d. grenzgeb. d. Med. u. Chir.*, 1911, xxii, 623; *Ibid.*, 1911, xlviii, 1973.

7. Wilson: *Brit. Jour. Child. Dis.*, 1913, x, 289. Jeffrey: *Quart. Jour. Med.*, 1910-1911, iv, 267.

vessels—the so-called transperietal route. This probably occurs, but gives rise to an infected kidney, not to pyelitis as we see it in infants. Pyelitis may follow this condition by secondary blood infection.

The usual mode of infection in pyelitis appears to be somewhat as follows: From the intestinal tract or some other source bacteria get into the lymphatic vessels and then into the blood, or possibly directly into the blood. They are transferred by the blood to the kidney. After reaching the kidney they pass through the glomeruli and are excreted at the pelvis. They may pass out of the body in the urine without doing any damage, or they may set up an infection at their point of excretion, that is, produce a pyelitis. They may during their passage through the kidney cause more or less damage to the various portions of the organ. Which of the alternatives occurs within the kidney depends on the virulence and character of the bacteria and on the resistance of the individual and of the local tissues. The colon bacillus, being of comparatively low pathogenicity, causes almost no damage to the kidney substance in its passage through the organ. An infection of the kidney may take place by extension inward from the pelvis, probably by lymphatic channels. This infection causes a greater or less degree of permanent damage to the substance of the kidney and presents a complication of, or sequel to, the usual pathology of the disease. The various stages in this process as outlined in the foregoing statement have been well established.

Blood infection in nearly all the acute infectious diseases is now so well known that no proof needs to be given in its support. The colon bacillus has been found in the blood by several investigators.⁸ Crabtree found that organism in the blood in seven out of nine patients who developed pyelitis under observation. The blood infection was always early in the disease, disappearing later, as in typhoid fever.

The intestinal tract is the most likely source of the infection in the majority of cases of pyelitis, especially in those due to the colon bacillus. Calmette⁹ and many others¹⁰ have shown that pigment par-

8. Crabtree: *Lancet-Clinic*, 1916, cxv, 96. Moser: *Deutsch. Ztschr. f. Chir.*, 1915, cxxxii, 71. Ruediger: *Philippine Jour. Sc.*, 1915, x, 25.

9. Calmette: *Ann. de l'Inst. Pasteur*, 1905, xix, 601; *ibid.*, 1906, xx, 353, 609; *Compt. rend Soc. de biol.*, 1906, lxi, 161, 548.

10. Among these may be cited the following:

Arbeiter: *Virchows Arch. f. path. Anat.*, 1910, cc, 321.

Whitla and Symmers: *Brit. Med. Jour.*, 1908, ii, 61.

Nichols: *Jour. Med. Research*, 1904, xii, 455.

Ford: *Tr. Assn. Am. Phys.*, 1900, xv, 389.

Adami: *Montreal Med. Jour.*, 1898, xxvii, 485; 1902, xxxi, 105.

Cobbett: *Jour. Path. and Bacteriol.*, 1910, xiv, 563.

Griffith: *Royal Commission on Tuberculosis, Second International Report*, 1907, Appendix 1, 628, 696.

Ravenel: *Jour. Med. Research*, 1903, x, 460.

Ravenel and Reichel: *Jour. Med. Research*, 1908, xviii, 1.

ticles, tubercle bacilli and other bacteria are carried with the fat from the intestinal canal in the lymph vessels of the mesentery during digestion and are distributed by the blood to all parts of the body, including the kidney. Other writers have called attention to the passage of the colon bacillus through the damaged intestinal mucous membrane,¹¹ and to the frequent association of pyelitis with constipation and other digestive disturbances.¹² Ten Broeck¹³ found organisms of the colon bacillus group post mortem in the heart's blood of five out of fourteen patients dying of infectious diarrhea and in the ileocecal lymph nodes in five cases. Trumpp¹⁴ found colon bacilli in the urine of fourteen out of seventeen children with follicular enteritis. Morse¹⁵ and Knox¹⁶ include cases of pyelitis in their reports of urinary analyses in gastro-intestinal diseases. Kowitz¹⁷ has emphasized the seasonal incidence of pyelitis following the diarrheas of summer. Edith Williams¹⁸ found in urine cultures of seventy consecutive cases that of forty-four patients with chronic intestinal disorders, sixteen showed colon bacilli. The importance of considering the gastro-intestinal tract in the treatment of pyelitis has been emphasized by many writers¹⁹ and is well known to all who have had experience with the disease. MacGowan²⁰ says he has seen a direct rise and fall of the bacilli in the urine with the neglect or care of the bowels.

Undoubtedly, there are sources of infection other than the gastro-intestinal tract, such as the teeth, tonsils and local septic lesions. Several writers²¹ have emphasized this and the necessity of finding and

11. Park: *Tr. Am. Surg. Assn.*, 1893, xi, 213. French: *Brit. Med. Jour.*, 1908, i, 1029. Thiemich: *Jahrb. f. Kinderh.*, 1910, lxxii, 243.

12. Brennemann: *Jour. Am. Med. Assn.*, 1911, lxi, 631. Friedenwald: *Arch. Pediat.*, 1910, xxvii, 801. Dudgeon: *Lancet*, London, 1908, i, 615. Green: *Boston Med. and Surg. Jour.*, 1913, clxviii, 645. Cannato and Caronia: *Pediatrics*, 1914, xxii, No. 9. Langstein: *Med. Klin.*, 1913, ix, 1491. Zobel: *Jour. Am. Med. Assn.*, 1916, lxvi, 496. White, W. H.: *Lancet*, London, 1912, ii, 1204.

13. Ten Broeck: *Boston Med. and Surg. Jour.*, 1915, clxxiii, 284.

14. Trumpp: *Jahrb. f. Kinderh.*, 1897, xlv, 268.

15. Morse and Crothers: *Arch. Pediat.*, 1909, xxvi, 561.

16. Knox and Meakins: *Arch. Int. Med.*, 1908, ii, 241.

17. Kowitz: *München. med. Wchnschr.*, 1914, lxi, 1341.

18. Williams, E.: *Lancet*, London, 1912, ii, 511.

19. Among these may be cited the following:

Pardoe: *Brit. Med. Jour.*, 1910, ii, 1129.

Briscoe: *Lancet*, London, 1909, ii, 1269.

Hutchinson: *Clin. Jour.*, 1911, xxxviii, 209.

Thompson, W. H.: *Med. Rec.*, New York, 1910, lvii, 907.

Pringle: *Practitioner*, London, 1911, lxxxvii, 35.

Jeffreys: *Quart. Jour. Med.*, 1911, iv, 267.

20. MacGowan: *Jour. Am. Med. Assn.*, 1915, lxiv, 226.

21. Rawles: *Med. Rec.*, New York, 1911, lxxx, 707; *Ibid.*, 1912, lxxxii, 359. Smith, F. H.: *Old Dominion Jour. Med. and Surg.*, 1914, xix, 77. Nice: *South. Med. Jour.*, 1915, viii, 1027. Grulee and Gaarde: *Jour. Am. Med. Assn.*, 1915, lxv, 312. Huet: *Nederl. Tijdschr. v. Geneesk.*, 1916, p. 521, abstr. *Jour. Am. Med. Assn.*, 1916, lxvi, 993.

removing the source of infection. The extra-intestinal sources are especially important in those cases in which the organism is some other than the colon bacillus. A patient of mine well illustrates this point: An infant 2 days old had a high temperature, a few impetiginous pustules on the neck and a pyelitis. The organism in the pustules was *Staphylococcus aureus* and the same organism was in the urine. After the healing of the skin lesions the pyelitis quickly disappeared.

The work of Kraus²² has shown definitely that bacteria may pass through the kidney without causing lesions in its substance. If staphylococci are injected into the ear of a rabbit, they cause lesions in the heart, abdominal wall and pyramids of the kidney passing through the glomeruli without setting up inflammation. Honeij²³ found leprosy bacilli in the urine of patients during the febrile stage of the disease. Brown,²⁴ Rist and Kindberg²⁵ and Foulerton and Hillier²⁶ found tubercle bacilli in the urine of patients whose kidneys were not damaged. Crabtree has injected the paratyphoid organism into the rabbit and recovered it from the urine. At necropsy the kidneys were normal.

The infection of the pelvis of the kidney from within, that is, by bacteria brought to it by the blood and excreted, seems established.

The possibility of the infection of the kidney substance from infection in the pelvis was shown by Kumita,²⁷ who demonstrated the extensive lymphatic connection between all parts of the kidney. That such infection actually occurs has been demonstrated by Hugh Cabot and Crabtree²⁸ and supported by A. Müller.²⁹

This statement of the mode of infection in pyelitis satisfies all the conditions except in offering an explanation for the greater frequency of the disease in females. This explanation is not hard to find, for no mention has been made of a very important source of lymphatic and blood infection of the kidney, namely, the pelvic organs. Poirier³⁰ and Sobotta³¹ have shown that the lymphatic vessels draining the pelvic organs are connected by free anastomosis with the kidney. These vessels drain through the thoracic duct into the blood. Sweet and Stewart³² proved experimentally that when the ureters were cut and sewed into the intestinal canal, if infection of the kidneys occurred,

22. Kraus: Arch. f. exper. Path. u. Pharmakol., 1896, xxxvii, 1.

23. Honeij: Jour. Infect. Dis., 1915, xvii, 376.

24. Brown, L.: Jour. Am. Med. Assn., 1915, lxiv, 886.

25. Rist and Kindberg: Presse med., 1914, xxii, 177.

26. Foulerton and Hillier: Brit. Med. Jour., 1901, i, 774.

27. Kumita: Arch. f. Anat. u. Path., Anat. Abt., 1900, xlix, 94.

28. Cabot, H., and Crabtree: Unpublished communication.

29. Müller: Ztschr. f. Urol., 1912, Supplement.

30. Poirier: The Lymphatics, Constable, London, 1903, Translation by Leof.

31. Sobotta: Human Anatomy, 1907.

32. Sweet and Stewart: Surg., Gynec. and Obstet., 1914, xviii, 460. Stewart: Univ. Penn. Med. Bull., 1910, xxiii, 233.

TABLE 1.—DETAILED RECORD OF THE CULTURES MADE FROM THE SECRETIONS
OF THE VAGINA IN GIRLS OF VARIOUS AGES

Case	Age	No Growth	Staph- ylococci	Strepto- cocci	Gram- Negative Bacilli	Colon	Other Organisms
1	2 hours.....	+					
	30 hours.....	..	+	..	+		
2	6 hours.....	+					
	34 hours.....	..	+				
3*	6 hours.....	+			
	6 hours.....	+			
	13 days.....	..	+	+	+		
4	22 hours.....	+			
5	7½ hours.....	+					
	8 days.....	..	+	+			
6	2 days.....	..	+				
	11 days.....	..	—	—	+		
7	3 days.....	..	+	Spore bearing gram. neg. bac.
8	4 days.....	..	+	..	+		
	9 days.....	..	+	..	+		
9	2½ hours.....	+					
	2 days.....	..	+	..	+		
	5 days.....	..	+				
	8 days.....	+			
10	7 hours.....	+					
	3 days.....	..	+	+	Gram positive bac.
	6 days.....	..	+				
11	8 days.....	..	+				
12	2 days.....	..	+				
	5 days.....	..	+	..	+		
	8 days.....	..	+	+	
13	18 hours.....	..	+	+			
	4 days.....	..	+	+			
14	7 hours.....	+					
	3 days.....	+			
15	2 days.....	..	+	..	+		
	5 days.....	..	+				
16	24 hours.....	+					
17	3 years.....	+			
	3 years.....	+			
	5 years.....	+			
	3 years.....	+		

* Secretion taken from the vulva.

+ Secretion taken from the urethra.

TABLE 1.—DETAILED RECORD OF THE CULTURES MADE FROM THE SECRETIONS OF THE VAGINA IN GIRLS OF VARIOUS AGES—(Continued)

Case	Age	No Growth	Staphylococci	Streptococci	Gram-Negative Bacilli	Colon	Other Organisms
18	8 months.....	+	+		
	8 months.....	..	+	+	
19	6 years.....	Gram negative diplococcus
	6 years.....	+	
	6 years.....	+	Gram negative diplococcus
†	6 years.....	Gram negative diplococcus
20	2 years.....	+	+		
	2 years.....	+	+		
21	8 years.....	..	+				
22	8 years.....	+			
23	2 months.....	+	
24	6 months.....	..	+	+	..	+	
	6 months.....	+	
	6 months.....	+	
25	5 years.....	+		
26	16 months.....	+	
27	3 months.....	Bacillus fluores-
28	4 months.....	eens?
29	3 weeks.....	+			Bacillus fluores-
30	1 week.....	..	+	+			eens?
31	6 days.....	+					
32	6 days.....	..	+	+			
33	5 days.....	+	
34	5 years.....	+	
*	5 years.....	+	
35	2 years.....	+	
†	2 years.....	+			
36	11 months.....	..	+	+			
†	5 years.....	..	+	+			
37	8 months.....	..	+	+			
	5 years.....	+			
38	7 months.....	+	
39	4 months.....	+	
40	3 weeks.....	+		
	Total.....	8	29	29	14	13	

* Secretion taken from the vulva.

† Secretion taken from the urethra.

it was through the lymphatics about the ureters not through the lumen of the ureter. Sakata,³³ Sugimura,³⁴ Bauereisen,³ J. Thomson,³⁵ W. B. Clarke,³⁶ and Eisendrath and Kahn,³⁷ working on the problem of kidney infection, all come to the same conclusion, that the lymphatics, not the ureters, play the major rôle in conveying direct infection from the pelvic organs to the kidney. If bacteria get into the lymphatics, they may get into the blood through the thoracic duct and thus to the kidney, or possibly into the blood from the infection in the kidney, and cause a pyelitis. Thiele found bacteria in the blood and urine from pelvic infection. Cases of pyelitis following circumcision have been reported by many writers. Rovsing³⁸ in 1897 reported several cases of pyelitis in young married women, following rupture of the hymen. The female genital organs, with the close proximity of the urethra, vulva and vagina to the rectum and the semi-closed character of the parts, offer every advantage for the entrance and growth of colon bacilli and other bacteria.

To see whether this region was in fact a possible source of infection, I have made seventy-one cultures from the vagina, vulva or urethra of forty infants and young children. One infant 6 hours old and all over 18 hours old, except one infant 6 days old, showed a growth from vaginal culture. All the vulval and urethral cultures were positive. The first organisms to appear were streptococci and staphylococci and then small bacilli—not colon. Colon bacilli were found in vaginal cultures of infants as early as the fifth day.

The colon bacillus was identified by the following characteristics: motile bacillus, gram negative, obtained from characteristic (shiny, dirty, brown, confluent) colony on agar, giving acid coagulation of litmus milk, forming gas in glucose, and producing characteristic (as above) growth on potato.

The other bacillus frequently found was delicate, nonmotile, gram negative, causing no change in litmus milk, forming no gas in glucose and easily outgrown even by streptococci.

These findings are in accord with Schmidgall,³⁹ who found the vagina of newborns sterile ten out of thirteen times, and by the second day a profuse growth of cocci. The colon bacillus was isolated twelve times out of twenty-one in newborns after the second day. She

33. Sakata: *Arch. f. Anat. u. Physiol., Anat. Abt.*, 1903, 1.

34. Sugimura: *Virchows Arch. f. path. Anat.*, 1911, xx, 206.

35. Thomson, J.: *Quart. Jour. Med.*, 1909-1910, iii, 251.

36. Clarke, W. B.: *Clin. Jour.*, 1911, xxxviii, 177. Walker: *Lancet*, London, 1913, i, 435.

37. Eisendrath and Kahn: *Jour. Am. Med. Assn.*, 1916, lxvi, 561.

38. Rovsing: *Ann. d. mal. d. org. génito-urin.*, 1897, xv, 897, 1009, 1121, 1251; *Ibid.*, 1898, xvi, 179, 278.

39. Schmidgall: *Beitr. z. Geburtsh u. Gynäk.*, 1914, xix, 190.

showed also that the vaginal secretions did not kill off the pathogenic organisms. Others⁴⁰ have found bacilli and cocci in the vagina and vulva of infants in differing proportions. Alsberg in adults found the colon bacillus in 100 per cent. of cases in the urethra of women and concludes that it is a regular habitant of the female urethra.

A possible source of infection with colon bacilli or other bacteria is certainly present in the female vulva, urethra and vagina, and a slight trauma might easily accomplish the entrance of organisms into the lymphatic vessels and blood and thus permit their transportation to the kidney.

I think that we have sufficient evidence to believe that pyelitis is always a blood infection and that the bacteria frequently gain entrance to the blood by the lymphatics. In the uncomplicated cases the lesion remains localized in the pelvis of the kidney, where the organisms are excreted. Secondary infection of the kidney substance may occur by lymphatic channels from the pelvis. Quite possibly these secondary infections account for many "relapses." The source of the infection in the majority of cases, considering males and females together, is the gastro-intestinal tract. Some cases may arise from infection in the skin, teeth or tonsils or in some local septic process. Many cases in females, accounting for the greater number in this sex as compared with the males, arise from bacteria entering the blood, often via the lymphatics, from the urethra, vulva or vagina,

I wish to express my thanks to Dr. Franklin S. Newell for his kindness in permitting me to make cultures from infants at the Boston Lying-In Hospital, and to Dr. Richard S. Eustis and Dr. John W. Hammond, Jr., for assistance in the laboratory.

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40. Among these may be cited the following:

Menge: *Deutsch. med. Wchnschr.*, 1894, xx, 867.

Strognoff: *Monatschr. f. Geburtsh u. Gynäk.*, 1895, ii, 365.

Vahle: *Ztschr. f. Geburtsh u. Gynäk.*, 1895, xxxii, 368.

Knapp: *Monatsch. f. Geburtsh u. Gynäk.*, 1897, v, 84.

Neujean: *Beitr. z. Geburtsh u. Gynäk.*, 1906, x, 408.

41. Alsberg: *Arch. f. Gynäk.*, 1910, xc, 255.

ACETONE BODIES IN THE BLOOD OF CHILDREN *

FRED MOORE, M.S., M.D.

DES MOINES

In the literature of recent years many articles are to be found relating to acidosis, acetonuria, and acetonemia in children. These terms frequently are used synonymously, and many widely different conditions are described under these headings. In all reports of acetonemia that I have found various conditions are described in which the urine is characterized by the presence of acetone and diacetic acid. With the exception of Marriott's¹ papers I have found no records of the determination of acetone bodies (beta-oxybutyric acid, aceto-acetic acid, and acetone) in the blood of living children. This work was undertaken to determine the amount of acetone bodies in the blood of normal children and of children in various pathologic conditions, especially those with evidence of acidosis, such as, increased pulmonary ventilation, decreased carbon dioxid tension of the alveolar air, diminished alkali reserve of the blood serum and abnormal acidity of the urine.

The analyses of the blood were made according to Marriott's¹ modification of Shaffer's oxidation method for determining acetone bodies in the urine. One cubic centimeter of blood is sufficient for accurate estimation. The results are expressed in milligrams of acetone per 100 gm. of blood. In some cases the acetone bodies in the urine were also determined and the results are expressed in grams of acetone. When sufficient quantities of urine were available, the acetone was estimated as in Shaffer's method.² When only small quantities were available, the urine was oxidized in the usual way and the reading made in the nephelometer, as in the blood analyses.

In Table 1 are the findings in sixteen normal children, arranged according to their ages. These were dispensary patients suffering from a variety of minor troubles and were essentially normal as far as their nutrition was concerned. All were afebrile when the blood was taken. The ages varied from 5 weeks to 5 years. The average total acetone content of the blood was 6.3 mg. per 100 gm. The minimum quantity found was 0.8 mg. and the maximum was 13 mg. These extremes speak for the variation in the normal child. Marriott¹ reported deter-

* Submitted for publication April 28, 1916.

* From the Harriet Lane Home and from the Department of Pediatrics of the Johns Hopkins University.

1. Marriott: *Jour. Biol. Chem.*, 1913, xvi, 293; *Ibid.*, 1914, xviii, 507.

2. Shaffer: *Jour. Biol. Chem.*, 1908, v, 211.

minations of acetone bodies in the blood of six normal children from 5 to 10 years of age. He found an average total of 3.7 mg. per 100 gm.

TABLE 1.—ACETONE BODIES IN THE BLOOD OF NORMAL CHILDREN EXPRESSED AS MILLIGRAMS IN 100 GRAMS

Case Number	Age	Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total Acetone Bodies	Beta Ratio	Remarks
1	5 wk	2.5	4.4	6.9	63	Breast fed
2	6 wk.	1.4	1.3	2.7	48	Breast fed
3	7 wk.	0.3	0.5	0.8	62	Breast fed
4	11 wk.	0.7	0.6	1.3	46	Breast fed
5	4 mo.	2.1	1.2	3.3	33	Mixed feeding, breast and cow's milk
6	4 mo.	2.0	11.0	13.0	84	Mixed feeding
7	6 mo.	0.8	1.1	1.9	57	Mixed feeding
8	6 mo.	2.7	5.4	8.1	66	Breast fed
9	16 mo.	1.9	1.4	3.3	42	General diet
10	2 yr.	1.4	1.9	3.3	58	General diet
11	2½ yr	3.9	8.8	12.7	69	General diet
12	3 yr.	1.8	3.0	4.8	62	General diet
13	3 yr.	3.7	5.6	9.3	60	General diet
14	3 yr.	3.9	3.6	7.5	48	General diet
15	3 yr.	5.3	6.8	12.1	56	General diet
16	4 yr.	4.0	5.8	9.8	60	General diet
Minimum.....		0.3	0.5	0.8	33	
Maximum.. ..		5.3	11.0	13.0	84	
Average.....		2.4	3.9	6.3	57	

Starvation has long been recognized as a cause of acetonuria. The frequency of the acetone reaction in the urine of children with widely differing diseases indicates the mild degree of metabolic disturbance which may cause the excretion of acetone bodies. For example, Frew³ reported that from 60 to 65 per cent. of the urines of 662 patients admitted consecutively to the Great Ormond Street Hospital gave positive tests for acetone when examined by the sodium nitroprussid test, according to Rothera's⁴ method. He concluded that the disease from which the child was suffering had less to do with the appearance of acetone bodies than the dietetic changes incident to admission to the ward. The latter are especially important because

3. Frew: *Lancet*, London, 1911, ii, 1264.

4. Rothera: *Jour. Physiol.*, 1908, xxxviii, 491.

of the large number of children who are partly or completely starved for a time after admission, either through voluntary refusal or restricted feeding.

One case afforded me an opportunity to estimate the blood acetone in a normal starving infant. A normal child of 20 months who had refused everything except the breast was admitted to the hospital to be weaned. She had been exclusively breast fed and refused all food for forty-eight hours after admission. After two days of voluntary starvation the blood was examined and found to contain 39.5 mg. of acetone bodies per 100 gm. of blood. The child was irritable, but there were neither signs of disease nor evidence of acidosis.

The results in six cases of marked eczema are recorded in Table 2. These children ranged from 1 month to 3 years of age. One child of 3 years had a very small amount, 1.3 mg. per 100 gm.; another, 8 months of age, showed an amount equal to that of the normal nursing, that is, 5.2 mg. per 100 gm. The others showed some increase, giving an average of 10.3 mg., a little less than twice the normal.

TABLE 2.—ACETONE BODIES IN THE BLOOD OF CHILDREN WITH ECZEMA
EXPRESSED AS MILLIGRAMS PER 100 GRAMS

Case Number	Age	Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total Acetone Bodies	Beta Ratio	Remarks
17	1 mo.	4.8	12.5	17.3	72	Breast fed 2 weeks; condensed milk 2 weeks Fed on cow's milk formula
18	5 mo.	3.6	6.2	9.8	63	
19	8 mo.	7.4	9.1	16.5	55	
20	8 mo.	1.7	3.5	5.2	67	Died within 12 hrs. after blood was taken Had had eczema constantly since 1 month of age
21	2½ yr.	6.7	
22	3 yr.	0.6	0.7	1.3	53	
Average.....		4.1+	6.4	10.5	62	
Minimum.....		0.6	0.7	1.3	53	
Maximum.....		7.4	12.5	17.3	72	

Table 3 includes five cases of acute infection with marked febrile reaction. It has long been recognized that with acute infectious diseases it is the rule to find acetone bodies in the urine. Their presence is so uniform that it is of no service in differential diagnosis. The amount determined by urinary analysis is not large, and, contrary to the opinion which was entertained at one time, it is now believed that the acetonemia does not add to the severity of the disease. This belief is justified by the findings that I have obtained in three cases of pneumonia, one of

TABLE 3.—ACETONE BODIES IN THE BLOOD OF CHILDREN WITH ACUTE FEBRILE DISEASE EXPRESSED AS MILLIGRAMS PER 100 GRAMS

Case Number	Age	Acetone + Diacetyl Acid	Beta-oxybutyric Acid	Total Acetone Bodies	Beta Ratio	Clinical Diagnosis	Remarks
23	11 mo.	6.9	15.0	21.9	68	Pneumonia.....	Temperature, 104; blood examined on fifth day; uneventful recovery
24	1 yr.	7.2	15.4	22.6	66	Pneumonia.....	Fatal result
25	3 yr.	5.0	18.0	23.0	78	Empyema.....	Recovery
26	2 yr.	7.8	5.7	13.5	42	Pneumonia with acidosis	Blood examined before alkali administration; rapidly progressive to fatal termination
26	2 yr.	3.4	13.6	17.0	80	Alkali intravenously; blood taken 15 minutes after respiration ceased; 35 c.c. urine contained 30 mg. acetone bodies
27	6 mo.	1.8	9.6	11.4	84	Pyelonephritis.....	Necropsy: Multiple abscesses of both kidneys

empyema and one of pyelonephritis. The acetone bodies were increased but not to a degree sufficient to cause clinical symptoms or laboratory findings pointing to acidosis. Nor was the amount sufficient to interfere in any way, so far as can be demonstrated at the present time, with metabolic processes. All the children (except the child in Case 26, Table 3) were taking food but an amount rather less than usual. The febrile reaction temperature varied from 103 to 105 F. It is noteworthy that three of the patients with pulmonary disease had nearly the same amount of acetone bodies and that this was much less than that found in the afebrile patient suffering from voluntary starvation. Case 24 terminated fatally. Case 26 gave evidence clinically of acidosis, as indicated by an increased pulmonary ventilation, which was corroborated by the demonstration of an increased hydrogen ion concentration in the blood serum and a decreased alkalinity of the blood as shown by Sellards' test. The acetone bodies in this patient, however, were very slightly increased. They were less than in the other patients with pneumonia which presented no evidence of acidosis. The child passed only 35 c.c. of urine during the twelve hours that he was in the hospital. This contained approximately 1 mg. of acetone bodies per cubic centimeter of urine. The amount of these bodies was not sufficient in any way to account for the marked evidences of acidosis that he presented. The acidosis must have been due to an accumulation in the blood of other acids. The course of the disease was rapidly progressive and the patient died about twelve hours after admission.

The cases included in Table 4 were cases of diarrhea. Six of the children were suffering from diarrhea with acidosis of the type described by Howland and Marriott.⁵ The acetone bodies in the blood were increased in all of these cases but only moderately so (11.1, 35, 10.2, 19 and 21.3 mg. per 100 gm. blood). This increase of the acetone bodies in such cases probably plays a minor part in the production of acidosis. This is well shown by the fact that other patients with diarrhea, but with no evidence of acidosis by laboratory tests, had quite as high an acetone body content in the blood. The table demonstrates this. Thus, the results of analyses in four cases were 14.4, 15.7, 22.8 and 30.3 mg. per 100 gm. of blood. With ileocolitis, on the other hand, I have found, in at least two cases, a large amount of acetone bodies in the blood. With one child the amount varied greatly from day to day. The large amount of 138.6 mg. per 100 gm. was determined on one occasion. Until further observations have been made it is impossible to say whether the increase in ileocolitis is due merely to the greater prolongation of an insufficient diet or whether something of a more specific nature plays a rôle.

5. Howland and Marriott: *Bull. Johns Hopkins Hosp.*, 1916, xxvii, 63.

TABLE 4.—ACETONE BODIES

Case No.	Age	Date	In the Blood, Expressed as Mg. Acetone per 100 Gm. Blood				Clinical Diagnosis	In the Urine, Expressed as Grams of Acetone				Remarks
			Acetone + Diacetic Acid	Beta-oxo-butyric Acid	Total	Beta Ratio		Acetone + Diacetic Acid	Beta-oxo-butyric Acid	Total	Beta Ratio	
28	8 mo.	5/29	2.3	8.8	11.1	77	Diarrhea with acidosis	Urine negative for acetone
29	7 mo.	6/ 7	11.0	24.0	35.0	68	Diarrhea with acidosis	0.012	0.019	0.031	61	Before giving alkali
29	7 mo.	6/ 8	0.045	0.088	0.133	60	After giving alkali
30	15 mo.	7/20	4.4	5.8	10.2	56	Diarrhea with acidosis					
31	7½ mo.	7/15	22.0	..	Diarrhea with acidosis					
32	6 mo.	6/13	21.3	..	Diarrhea with acidosis					
33	3 mo.	8/ 5	19.0	..	Diarrhea with acidosis					
34	10 mo.	11/13	11.4	..	Fatal diarrhea without acidosis					
34a	22 mo.	7/10	15.7	..	Fatal diarrhea without acidosis					
35	7 mo.	7/ 6	22.8	..	Fatal diarrhea without acidosis					
36	5 mo.	7/ 2	30.3	..	Fatal diarrhea without acidosis					
37	2 yr.	3/13	16.7	11.9	28.6	41	Ulcero colitis.....	0.198	0.700	0.898	77	Urine in 20 hr., 130 c.c., before alkali
37	2 yr.	3/14	0.333	1.275	1.608	79	Urine in 12 hr., 140 c.c.; alkali treatment
37	2 yr.	3/16	72.6	66.0	138.6	47	1.776	4.675	6.451	72	Urine in 20 hr., 450 c.c.; 140 mg. acetone per 100 c.c. urine
37	2 yr.	3/17	0.633	1.735	2.368	73	Urine in 20 hr., 250 c.c.
37	2 yr.	3/18	2.356	5.482	8.038	70	Urine in 24 hr., 515 c.c.
37	2 yr.	3/19	58.7	62.1	110.8	47	1.520	3.363	4.883	68	Urine in 18 hr., 410 c.c.; 110 mg. acetone per 100 c.c.
37	2 yr.	3/23	52.8	23.7	76.5	30	Acetonuria
38	8 mo.	4/16	7.4	9.1	16.5	55	Ulcero colitis.....	
38	8 mo.	4/17	51.7	130.9	182.6	71	0.051	0.160	0.211	75	Urine in 28 hr., 45 c.c.

Table 5 shows that in the cases with which there is apparently a spontaneous formation of acetone bodies the amount of these found in the blood is often large. One child of 3 years, who died after an illness of only seventy-two hours, had 170 mg. per 100 gm. of blood. Another, of 3 years, with 88 mg. per 100 gm. of blood recovered after an illness of five days, while a third, 14 months old, who had been ill for three days, died. On the third day of illness he had 136 mg. of the acetone bodies per 100 gm. of blood. The amount is thus seen to be greatly in excess of that found with ordinary acute diseases and approaches closely to the amount (240 mg.) that I found in a fatal case of diabetic coma in an adult. The mechanism for the rapid formation of the acetone bodies in these apparently spontaneous cases is quite unknown and cannot even be suggested at present.

Two cases of diabetes mellitus (Table 6) in boys of 3 and 8 years afforded opportunity to make parallel determinations of the blood acetone and the acetone bodies excreted in the urine. Both showed very mild symptoms of acidosis when admitted. They responded quickly to starvation treatment. They rapidly became sugar free and showed a marked reduction in the acetone output. The younger boy proved to have a more severe form of diabetes and his blood acetone did not diminish under treatment as did that of the other. As the diet was increased his blood acetone increased almost to the original amount, while that of the older boy was reduced from 50 to 20 mg. They show well that the amount of acetone bodies in the blood does not bear any constant relation to that excreted in the urine. On April 1 the blood acetone of the patient in Case 42 was 58.3 mg. and he excreted 3.674 gm., whereas the patient in Case 43 had a blood acetone of 50.9 mg. and excreted only 1.408 gm. acetone in the urine. On April 9 there was 10 per cent. difference in the amount of acetone bodies excreted while the difference in the blood was 50 per cent. On April 14 the patient in Case 42 had 2.7 times as much acetone bodies in the blood as the patient in Case 43 but his excretion of acetone bodies was actually less. Comparison of the blood acetone and urinary acetone of the same patient at different times also illustrates this fact. In considering the constantly increased blood acetone of the patient in Case 42, it should be stated that his tolerance for food was much less than that of the older patient. Neither of these patients presented any signs of acidosis after the first few days in the ward.

Neubauer⁶ first called attention to the proportion of beta-oxybutyric acid in the urinary excretion in some work on experimental acidosis and diabetic urines. This is expressed as the percentage of the total

6. Neubauer: *Verhandl. d. deutsch Kong. f. inn. Med.*, 1910, xxvii, 566.

TABLE 5.—ACETONE BODIES

Case No.	Age	Date	In the Blood, Expressed as Mg. Acetone per 100 Gm. Blood				Clinical Diagnosis	In the Urine, Expressed as Grams of Acetone			Remarks
			Acetone + Diacetic Acid	Beta-oxybutyric Acid	Total	Beta Ratio		Acetone + Diacetic Acid	Beta-oxybutyric Acid	Total	
37a	3 yr.	4/17	29.9	140.1	170.0	82	Recurrent vomiting...	0.086	0.205	0.291	Urine in 20 hr., 70 e.e.; fatal
38a	3 yr.	1/18	Renal tumor with spontaneous aceto-naemia	2.472	6.428	8.9	Incomplete 24 hr. specimen, 620 e.e.
39	14 mo.	1/9	136.0	..	Spontaneous aceto-naemia	Fatal
40	6 yr.	1/17	84.5	..	Recurrent vomiting...	Rapid recovery
41	3 yr.	2/9	88.5	..	Spontaneous aceto-naemia	Slow recovery

TABLE 6.—ACETONE BODIES

Case No.	Age	Date	In the Blood, Expressed as Mg. Acetone per 100 Gm. Blood				Clinical Diagnosis	In the Urine, Expressed as Grams of Acetone				Remarks
			Acetone + Diacetic Acid	Beta-oxybutyric Acid	Total	Beta Ratio		Acetone + Diacetic Acid	Beta-oxybutyric Acid	Total	Beta Ratio	
42	3 yr.	3/30	Diabetes mellitus.....	1.364	3.685	5.049	73	General diet
42	3 yr.	4/ 1	25.3	33.0	58.3	56	1.012	2.662	3.674	72	Green diet started
42	3 yr.	4/ 9	12.0	25.0	37.0	60	0.963	0.737	1.700	66	60 gm. oatmeal added to green diet
42	3 yr.	4/14	8.3	44.0	52.3	84	0.231	0.319	0.550	57	1 egg added to previous diet
43	8 yr.	3/30	Diabetes mellitus.....	0.943	2.470	3.383	73	General diet
43	8 yr.	4/ 1	20.9	30.0	50.9	60	0.396	1.012	1.408	71	Green diet started
43	8 yr.	4/ 3	0.429	0.286	0.715	40	
43	8 yr.	4/ 9	9.9	14.3	24.2	59	0.380	0.620	1.000	62	60 gm. oatmeal added
43	8 yr.	4/14	7.9	11.6	19.0	61	0.231	0.407	0.638	63	

acetone bodies in the urine and for convenience has been designated as the beta ratio. He observed that this ratio was from 60 to 80 per cent. in patients who were excreting several grams or more of acetone bodies. Others have given this point some consideration and recently Kennaway,⁷ in analysis of diabetic urines, has corroborated Neubauer's observation. In a series of about twenty examinations of the urines of the two diabetics referred to above I have found the same thing. A striking example of this is shown in the urinary analyses in Case 43, recorded in Table 6, in which the beta ratio dropped from 71 to 40 with a decrease of total acetone bodies from 1.408 gm. to 0.715 gm. The subsequent rise of total acetone bodies to 1 gm. is accompanied by a beta ratio of 62. The beta ratio in other cases of acidosis bore no such relation. Excluding the patient moribund from pneumonia (Case 26) it was not less than 60 per cent. in any case, and was as high as 70 per cent. in some instances when the total acetone excretion was very small. The beta ratio in the blood acetone shows wide variations and permits no definite conclusions. In general I have been unable to attach any significance to the beta ratio in either the blood or the urine.

SUMMARY

The blood of sixteen normal children was examined quantitatively for acetone bodies (beta-oxybutyric acid, aceto-acetic acid and acetone). Expressed as milligrams of acetone per 100 gm. of blood, this was found to vary from 1 to 13 mg., with an average of 6.3 mg.

The blood of a normal child after forty-eight hours of voluntary starvation was examined for acetone bodies and found to contain 39.5 mg. acetone bodies per 100 gm. of blood.

Acute febrile disturbances are accompanied by an increase in the blood acetone, though this may not be very marked.

In some patients showing acidosis clinically, the acetone content of the blood was found to be sufficient to account for the acidosis.

Many cases of acidosis in infancy and childhood are not accompanied by an increase of acetone bodies in the blood sufficient to account for the severity of the acidosis.

In a given case of acidosis acetonuria alone does not indicate that the acidosis is due to an increase of the acetone bodies in the blood. To determine this quantitative studies of the blood are necessary.

Equitable Building.

7. Kennaway: *Biochem. Jour.*, 1914, viii, 355.

TYPES OF PNEUMOCOCCUS FOUND IN THE PNEUMONIAS OF INFANTS AND YOUNG CHILDREN *

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Immunologic studies have illuminated both bacteriology and serology by proving that the majority of pathogenic bacteria belong to groups composed of various types which may be identified by their reactions in the serum of infected animals. Dochez and Gillespie¹ showed that the pneumococcus group comprises four types which have since been found in Germany as well as in this country. Two additional types of pneumococci apparently exist in South Africa.² Types 1, 2 and 3 have definite immunity reactions identical to all members of the group, while Type 4 comprises a number of independent varieties differing from Types 1, 2 and 3 and also from each other. Pneumococci of Type 4 are ordinarily present in the mouth in healthy persons who have not been in contact with lobar pneumonia patients, and cause only 20 to 25 per cent. of the disease. While pneumococci of this type may be possessed of great virulence, cases of lobar pneumonia in adults caused by such cocci are but rarely fatal. By far the greater number of cases of lobar pneumonia (80 per cent.) are due to pneumococci belonging to Types 1, 2 and 3. Types 2 and 3 are responsible for the highest death rate, and Type 1 causes a lower percentage of fatalities than either of the other two.

Thus far studies on only adult patients have been made, and lobar pneumonia alone has been considered. The interesting question of the types of pneumococcus present in the pneumonias of infancy naturally suggested itself, and such a study was undertaken at the Babies' Hospital during the past winter.

TECHNIC

The method of obtaining material by puncturing the lung was not found practicable in young children, whose pulmonary consolidation may be small and superficial in extent, and the puncture attended with danger of causing pneumothorax. This method was therefore practiced in only three cases. For the rest, the sputum was relied on. The child was made to cough and the expectorated material was collected on a swab, rubbed up in salt solution and injected into a white mouse.

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* From the Pathologic Laboratory of the Babies' Hospital, New York.

1. Dochez and Gillespie: Jour. Am. Med. Assn., 1913, lxi, 727.

2. Dochez and Avery: Jour. Exper. Med., 1915, xxi, 114.

The animals were killed after twenty-four hours if they had not died within that time, and the necropsy was performed at once, cultures being made on blood agar from the peritoneal exudate and from the heart's blood. With the pure growths thus obtained agglutination tests were made with antipneumococcus serum kindly furnished us by the Rockefeller Institute Hospital. No more rapid technic was employed because no attempt was made to treat these children with specific anti-serum and consequently no indication for haste existed.

CASES STUDIED

Fifty cases of respiratory disease were studied, the clinical diagnosis reading as follows:

Lobar pneumonia	11
Bronchopneumonia	36
Bronchitis	2
Postpneumonic empyema	1
Total.....	50

The age of the children varied from 25 days to 4½ years, as shown in the following tabulation:

Age	No.	Age	No.
Under one month.....	1	12 to 18 months.....	13
1 to 2 months.....	1	18 to 24 months.....	6
2 to 3 months.....	1	2 to 3 years.....	3
3 to 6 months.....	6	3 years	2
6 to 9 months.....	4	4½ years	1
9 to 12 months.....	12	Total.....	50

There were sixteen girls and thirty-two boys. The largest number of cases occurred during the month of December.

LOBAR PNEUMONIA

Analyzing the group of eleven lobar pneumonia patients, we find that the youngest was 6 months old and the oldest 3 years. Four were under 1 year, five were between 1 and 2 years and two were over 2 years of age. Four children died, all less than 18 months old.

LOBAR PNEUMONIA			
CURED		IMPROVED	
Age, Mo.	No.	Age, Mo.	No.
36	1	30	1
20	1	DIED	
17	1	17	1
14	1	15	1
10	1	11	1
7	1	6	1

The pneumococci present in these eleven cases are shown in Table 1. It will be seen that a pneumococcus of Type 1 was found in three cases, Type 2 twice, and Type 4 seven times, while in two instances no pneumococci were found.

TABLE 1.—BACTERIOLOGIC FINDING IN FIFTY CASES OF PNEUMONIA

Case Number	Diagnosis	Organism	Source				Result				
			Sputum	Pleural Puncture	Blood	Lumbar Puncture	Necropsy	Cured	Im- proved	Unim- proved	Died
46	Lobar pneumonia.....	Pneumococcus, Type 1..... Pneumococcus, Type 4.....	+	+	1			
43	Lobar pneumonia.....	Pneumococcus, Type 1..... Pneumococcus, Type 4.....	+	+	+	1
35	Lobar pneumonia.....	Pneumococcus, Type 1..... Pneumococcus, Type 4..... Staphylococcus aureus.....	+	+	1
45	Lobar pneumonia.....	Pneumococcus, Type 4.....	+	+	1			
10	Lobar pneumonia.....	Staphylococcus aureus..... Influenza.....	+	+	1		
1	Lobar pneumonia.....	Pneumococcus, Type 2.....	+	1			
15	Lobar pneumonia.....	Pneumococcus, Type 2..... Influenza.....	+	+	1			
2	Lobar pneumonia.....	Pneumococcus, Type 4.....	+	1
5	Lobar pneumonia.....	Pneumococcus, Type 4.....	+	1
22	Lobar pneumonia.....	Pneumococcus, Type 4.....	+	1			
6	Lobar pneumonia.....	Streptococcus (3 strains).....	+	1			
29	Bronchopneumonia.....	Pneumococcus, Type 1.....	+	1
41	Bronchopneumonia.....	Pneumococcus, Type 1.....	+	1
8	Bronchopneumonia.....	Pneumococcus, Type 1..... Staphylococcus aureus.....	+	1
17	Bronchopneumonia.....	Pneumococcus, Type 2.....	+	1
14	Bronchopneumonia.....	Pneumococcus, Type 2.....	+	1
4	Bronchopneumonia.....	Pneumococcus, Type 2..... Streptococcus.....	+	+	1			
32	Bronchopneumonia.....	Pneumococcus, Type 2..... Influenza.....	+	+	1			
7	Bronchopneumonia.....	Pneumococcus, Type 2.....	+	+	1			
9	Bronchopneumonia.....	Pneumococcus, Type 4.....	+	1
13	Bronchopneumonia.....	Pneumococcus, Type 4.....	+	1			
20	Bronchopneumonia.....	Pneumococcus, Type 4.....	+	1	

25	Bronchopneumonia.....	Pneumococcus, Type 1.....	+	1
27	Bronchopneumonia.....	Pneumococcus, Type 4.....	+	1
28	Bronchopneumonia.....	Pneumococcus, Type 1.....	+	1
37	Bronchopneumonia.....	Pneumococcus, Type 4.....	+	1
38	Bronchopneumonia.....	Pneumococcus, Type 1.....	+	1
40	Bronchopneumonia.....	Pneumococcus, Type 4.....	+	1
42	Bronchopneumonia.....	Pneumococcus, Type 1.....	+	1
44	Bronchopneumonia.....	Pneumococcus, Type 4.....	+	1
47	Bronchopneumonia.....	Pneumococcus, Type 1.....	+	1
50	Bronchopneumonia.....	Pneumococcus, Type 4.....	+	1
3	Bronchopneumonia.....	Pneumococcus, Type 1.....	+	+	1
49	Bronchopneumonia.....	Pneumococcus, Type 4.....	+	+	..	1	1
19	Bronchopneumonia.....	Pneumococcus, Type 1.....	+	+	1
18	Bronchopneumonia.....	Pneumococcus, Type 4.....	+	1
23	Bronchopneumonia.....	Pneumococcus, Type 1..... Staphylococcus aureus.....	++	1
16	Bronchopneumonia.....	Pneumococcus, Type 4..... Influenza.....	+	1
24	Bronchopneumonia.....	Pneumococcus, Type 4..... Influenza.....	+	1	1
12	Bronchopneumonia.....	Streptococcus.....	+	1
33	Bronchopneumonia.....	Streptococcus.....	+	1
11	Bronchopneumonia.....	Staphylococcus aureus.....	+	1
39	Bronchopneumonia.....	Staphylococcus aureus.....	+	1
48	Bronchopneumonia.....	Staphylococcus aureus.....	..	+	1
31	Bronchopneumonia.....	Influenza.....	+	1
39	Bronchopneumonia.....	Influenza.....	+	1
34	Bronchopneumonia.....	Influenza.....	+	1
21	Acute bronchitis.....	Pneumococcus, Type 1.....	+	1	1
36	Acute bronchitis.....	Streptococcus.....	+	1	1
26	Postpneumonic empyema.	Pneumococcus, Type 4..... Staphylococcus aureus.....	++	1	1
Totals.....						91	93

The children from whom Type 1 pneumococci were isolated present several interesting facts. In the first place, two of three died, and all three presented a Type 4 pneumococcus in addition to the strain belonging to Type 1. Two of the three patients, one of whom recovered, developed purulent fluid in the pleural cavity and the pneumococcus isolated from the pleural fluid proved, in both instances, to be of a different type from that isolated from the sputum. Thus, in one child 14 months old the cocci present in the sputum belonged to Type 1, and those from the pleural exudate to Type 4. Recovery resulted. In a fatal case on the other hand, in a patient 21 months old, the sputum contained cocci of Type 4, while from the blood and pleural fluid cocci identified as belonging to Type 1 were isolated. In another fatal case the cocci in the sputum belonged to Type 4, but at the necropsy a Type 1 pneumococcus was found in the consolidated lung.

These two cases naturally raise the question as to whether sputum cultures in young children are reliable for a study of this kind; that is, whether the pneumococci found in the material obtained from the mouth are identical with those present in the pulmonary lesion. Do these young infants, in the weakened condition incidental to a severe pneumonia, make effectual efforts at coughing, and do they really raise sufficient pulmonary exudate to make cultural tests from mouth material a proper index of the cocci in the lung? That this is the rule in adults we know; that it does happen in infants is proved by one of our three cases, but that it does not always happen is shown by two other cases. It is certainly a fact to be taken into consideration, and lung puncture, when possible, should be chosen as the method to obtain a reliable specimen for study of the bacteriologic content of an area of pulmonary consolidation.

In the case in which the pleural pus contained Type 4 pneumococcus and the sputum Type 1, it is quite possible that some cocci of both types were present in both sputum and pleural fluid, but that the colonies fished for the agglutination tests did not agree. Since the morphology and the biology of pneumococci belonging to Types 1, 2 and 4 are identical, the only way to prove this point would be to fish a large number of colonies from the plates sown with the material from the mouse's blood and peritoneal exudate, and then study all such cultures with the immune serums.

Two of the five patients with lobar pneumonia containing Type 4 pneumococcus died. Whether cocci of another type were also present remains an open question, since no necropsy was permitted. One of the children who recovered had Type 4 pneumococcus in the pleural fluid as well as in the sputum.

While the mortality of the lobar pneumonia patients in this series due to pneumococci of Type 4 was two out of five, or 40 per cent., in

the cases due to Type 1 it was two out of three, or 66⅔ per cent. One of the two children from whom Type 2 pneumococcus was isolated had *Bacillus influenzae* in the sputum at the same time; both recovered. We realize that the number of our cases of lobar pneumonia is very small, and that the bacteriologic results are to be considered as suggestive rather than conclusive.

Two patients with lobar pneumonia did not have any pneumococci in their sputum. But since both recovered the correctness of the clinical diagnosis must be open to question. The sputum from one of these children yielded a growth of streptococci on three separate tests, and one strain proved rather puzzling. Its morphology was that of a pneumococcus, quite different from the other two strains, but it did not ferment inulin and proved insoluble in bile and in optochin. It apparently agglutinated immune serum of pneumococcus Type 1 and Type 2 equally well, the control remaining smooth.³ The other two strains of streptococcus isolated from the sputum of this child proved to be very virulent for rabbits and dogs. The last case of the series gave a growth of *Staphylococcus aureus* and *Bacillus influenzae* from the sputum and of *Staphylococcus aureus* alone from the pleural pus. Since the child was discharged in an improved condition, there must be a doubt as to whether the pulmonary lesion was a true fibrinous pneumonia, as there is both clinical and experimental proof that bronchopneumonia, as well as lobar pneumonia, may be accompanied by empyema. Again the pneumococcus present in the lung may not have been present in the sputum, though this would seem less probable in the light of the presence of *B. influenzae* whose habitat is the smaller bronchi and so is often missed when only mouth secretions are planted, without successful attempts at cough and expectoration.

Summing up our eleven cases of lobar pneumonia, we find pneumococci of Type 1 present three times, always with Type 4; Type 2 twice; Type 4 alone four times; streptococcus once, and *Staphylococcus aureus* once. The four fatal cases all contained Type 4, and two had Type 1 as well. Four children had pus in the pleural cavity and of these, two died (Type 1) one recovered (Type 4,) and one (*Staphylococcus aureus*) improved.

Blood cultures in these eleven cases of lobar pneumonia were positive in only one case. Type 1 pneumococcus was found, and the baby died. This extremely low percentage of positive blood cultures is to be attributed to the fact that repeated cultures were not taken because of lack of time. The point as to whether a positive blood culture has a bad prognostic significance, as in adults, cannot be illuminated with these results.

3. This strain was submitted to Dr. Avery at the Rockefeller Hospital, who very kindly made the optochin test and pronounced the organism a streptococcus.

BRONCHOPNEUMONIA

Thirty-six cases of bronchopneumonia were studied, four of the children were suffering from tuberculosis as well. There were fourteen recoveries and eighteen deaths in the series, while one child left the hospital in an improved condition, and three were unimproved. The youngest infant, 25 days old, was admitted for tetanus neonatorum, the pneumonia contributing to the fatal outcome. The age and outcome of the bronchopneumonia cases is shown in the following tabulation, while the bacteria isolated from them are indicated in Table 1.

BRONCHOPNEUMONIA			
CURED		UNIMPROVED	
Age	No.	Age	No.
2 yr.	1	2 yr.	1
21 mo.	1	9 mo.	1
19 mo.	1	5 mo.	1
18 mo.	1	DIED	
16 mo.	1	19 mo.	1
14 mo.	1	15 mo.	1
13 mo.	3	14 mo.	1
12 mo.	1	13 mo.	1
9 mo.	2	11 mo.	2
7 mo.	1	9 mo.	5
6 mo.	1	5 mo.	1
		4 mo.	2
		3 mo.	1
		2½ mo.	1
		5 wk.	1
		25 days	1
IMPROVED			
4½ yr.	1		

Pneumococci of Type 1 were present in only three cases of bronchopneumonia, and all three patients died.

Type 2 pneumococci occurred in four children with two fatal results, one of which was complicated by tuberculosis. One of the two babies of this group who recovered had *B. influenzae* in his sputum; together with the pneumococcus, and the other had streptococci in addition to pneumococci.

Pneumococci belonging to Type 4 were present in twenty-one of the thirty-six cases of bronchopneumonia, or in 60 per cent. In twenty cases the cocci were isolated from the sputum, in two from the pleural fluid as well, and in one instance from the blood, cerebrospinal fluid, and sputum. Nine of these twenty-one infants died, nine recovered, one improved, and two were discharged unimproved. The high mortality rate of 43 per cent. is directly opposed to the mortality caused by Type 4 pneumococcus in the lobar pneumonia of adults, which is about 10 per cent. The low resistance of infants to infection in general is undoubtedly a factor in explaining the large percentage of pneumonias in infancy caused by the group of pneumococci ordinarily present in the mouth and also in explaining the high death rate.

In eighteen cases pneumococci of Type 4 were found in pure culture in the peritoneal exudate and blood of the inoculated mouse, while twice *B. influenzae* and once *Staphylococcus aureus* came through the circulation of the animals together with the pneumococci.

Most interesting is the fact that in this series of fifty children with pneumonia, only one developed a purulent leptomeningitis, and in this case pneumococci belonging to Type 4 were found in the sputum, blood, and cerebrospinal fluid during life, and in the blood and meningeal pus at necropsy.⁴ The pulmonary lesion was very limited and not severe; had it been more marked the general infection might not have occurred. This case also serves to emphasize the fact that in the bronchopneumonia cases in our series there was no discrepancy in the bacterial findings before and after death; that is, the cultures of the sputum and pleural fluids were identical with those made from the lungs at necropsy.

Streptococci were present in three cases of bronchopneumonia, once with a pneumococcus of Type 2. All of these children recovered, a fact which is to be noted.

Staphylococcus aureus was found in the sputum of six infants suffering from bronchopneumonia, of whom two recovered, one improved and three died. Two of the fatal cases were due to *Staphylococcus aureus* alone, while in the third a Type 1 pneumococcus was associated with it. Type 4 pneumococcus was found with the staphylococcus in two children, of whom one was cured and one improved. The higher mortality rate of the staphylococcus over the streptococcus pneumonias is striking.

B. influenzae appeared in the sputum in six cases of bronchopneumonia, three times in pure culture, with fatal results. It was associated with a Type 4 pneumococcus in two other patients, one of whom died, and with Type 2 pneumococcus in a child who got well. We wish to emphasize the fact that *B. influenzae* in pure culture always causes a bronchopneumonia, never a lobar pneumonia. When present with the pneumococcus in cases of lobar pneumonia it apparently does not modify the pulmonary lesion.

BRONCHITIS

Two cases were studied, one showing a Type 4 pneumococcus and one the streptococcus. Both patients recovered.

POSTPNEUMONIC EMPYEMA

A patient with empyema was admitted to the hospital after the antecedent pneumonia had run its course. Type 4 pneumococcus was

4. During the last few weeks a second case of leptomeningitis came to necropsy, and again Type 4 pneumococcus was isolated from the purulent exudate.

found in the sputum and *Staphylococcus aureus* in the pleural pus. The child improved and the nature of the original lesion remains obscure.

In four additional cases diagnosed as bronchopneumonia the sputum injected into white mice caused no illness in the animals, and no bacteria were found in the peritoneal fluid and blood when the mice were killed, twenty-four hours after inoculation. It is possible that only saliva and not lung exudate was injected, although the child made the usual attempts to cough. These cases serve to emphasize the disadvantage under which work of this kind suffers because of the dangers attendant on lung puncture in young children and the impossibility of obtaining material by that method. A parallel series of specimens of sputum and lung puncture material should be studied.

CONTROLS

Three controls were made with sputum from children who had no lesion in the respiratory tract, but who suffered from pyloric stenosis, rachitis, and malnutrition respectively. No one of the three resulted in positive cultures from the mice injected with a specimen of sputum; that is, the sputum of these three infants contained no bacteria which were pathogenic for white mice.

DISCUSSION

It will be seen that the findings in this series of pneumonias in young children are quite different from those reported by Dochez² and his associates in adult patients with lobar pneumonia. In infants bronchopneumonia is a more frequent disease than is lobar pneumonia, and in our series there were twenty-five infants under the age of one year, of whom 16 per cent. had lobar pneumonia and 80 per cent. had bronchopneumonia.

While in adult lobar pneumonias Type 4 pneumococcus is found in only from 20 to 25 per cent. of the cases, with a death rate of about 10 or 13 per cent., in infantile lobar pneumonia it was found in pure culture in 36 per cent. of the cases, though it was present in 63 per cent., with a death rate of 57 per cent. In bronchopneumonia cases, on the other hand, Type 4 pneumococcus occurred in pure culture in 50 per cent., though it was present in 60 per cent., with a mortality of 44 per cent. All the fatalities, strange to say, occurred among the cases in which this coccus was present alone. The three children in whose sputum other organisms were found did not die.

Type 2 pneumococcus was found in two patients, or 18 per cent. of the lobar pneumonia cases. Both children recovered, though one had *B. influenzae* in the sputum as well as the pneumococcus. In the babies with bronchopneumonia, Type 2 pneumococci were found in four, or

TABLE 2.—INCIDENCE OF TYPES 1, 2 AND 4 PNEUMOCOCCUS IN FIFTY CASES

Disease	In Pure Culture			With Type 4			With Staphylococcus Aureus			With B. Influenza		With Streptococcus		Number of Cases	Mortality, per Cent.	Average Mortality, Each Type, per Cent.
	Cured	Died	Unimproved	Cured	Died	Unimproved	Cured	Died	Unimproved	Cured	Died	Cure	Died			
Type 1: Lobar pneumonia..... Bronchopneumonia.....	0 0	0 2	0 0	1 0	2 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	3 3	66 100	83, Type 1
Type 2: Lobar pneumonia..... Bronchopneumonia.....	1 0	0 2	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	0 1	0 0	2 4	0 50	33, Type 2
Type 4: Lobar pneumonia..... Bronchopneumonia.... Bronchitis..... Postpneumonic empyema..	2 7 1 0	2 8 0 0	0 3 0 0	1 0 0 0	2 0 0 0	0 0 0 0	0 1 0 0	0 0 0 0	0 0 0 1	0 1 0 0	0 0 0 0	0 0 0 0	0 0 0 0	7 21 1 1	55 38 0 0	40, Type 4

11 per cent.; twice in pure culture, and twice with other organisms. The mortality rate it caused was nil in the lobar cases and 50 per cent. in the bronchopneumonias.

Type 1 pneumococcus occurred in three cases of lobar pneumonia, or 27 per cent., but never in pure culture; in all these cases Type 2 pneumococcus was also present. It caused a death rate of 66 per cent. In bronchopneumonia cases Type 1 pneumococcus was present in only three babies, all of whom died. Table 2 shows these figures, and it will be seen that Type 4 was present in thirty out of a total of fifty cases, or 60 per cent., with a mortality of 40 per cent., against a mortality of 33 per cent. caused by Type 2, and 83 per cent. caused by Type 1.

It seems fair to reason, then, that pneumococci of Types 1 and 2 are more likely to cause a lobar pneumonia in children, while Type 4 is more liable to produce a bronchopneumonia, though with a highly fatal course. Two facts are brought out by the study of this series of cases: (1) that the type of pneumococcus ordinarily present in the human mouth was the cause of 60 per cent. of all pneumonias in a series of fifty cases in young children, and (2) that the most frequent type of pulmonary lesion it produced was a bronchopneumonia, with a mortality of 43 per cent.

The fact that in children so many cases of pneumonia running a severe and even fatal course are due to Type 4 pneumococci cannot be without significance in the epidemiology of the disease. While the pneumococci ordinarily present in human mouths cause only 25 per cent. of lobar pneumonia cases in adults, they cause 60 per cent. of all pneumonias in children, thus serving to maintain the virulence of this type of coccus. In infants and young children Type 4 pneumococci cannot be looked on as innocuous.

Only two of eleven cases of lobar pneumonia failed to show the presence of pneumococci in the sputum, and since both of these children recovered, the correctness of the clinical diagnosis remains unproved. Of the thirty-six cases of bronchopneumonia, on the other hand, eight did not have any type of pneumococcus in the sputum.

In this series pneumonias due to the streptococcus ran a benign course, while *Staphylococcus aureus* caused a mortality which was higher than that due to Type 4 pneumococcus. *B. influenzae*, when present alone, proved fatal in three cases. This may be explained by the fact that only virulent strains of *B. influenzae* are capable of producing pulmonary consolidation, while the strains ordinarily present in the mouth and bronchi together with other organisms are, as a rule, of very low virulence.

SUMMARY

In this series of fifty cases of pneumonia in young children, the comparative frequency (60 per cent.) of Type 4 pneumococcus is noticeable, as is also the high mortality (40 per cent.) rate it caused.

Pneumococci of Types 1 and 2 were present in a higher percentage of lobar pneumonias than of bronchopneumonias; the mortality rate of the cases in which Type 1 was found reached 83 per cent., and Type 2 was fatal in 33 per cent. of the cases in which it occurred. All these figures are much higher than in lobar pneumonia cases in adults, and the greater mortality of Type 1 over Type 2 is also to be noted.

OBSERVATIONS ON THE INTRADERMAL AND REPEATED INTRADERMAL INJECTION OF DIPHTHERIA TOXIN WITH REFERENCE TO THE SCHICK TEST *

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The knowledge of the effect of subcutaneous and, inadvertently, intradermal injection of diphtheria toxin on the cutaneous tissue, is as old as the knowledge of diphtheria antitoxin. It was necessarily one of the first observations made during the process of immunization and of testing out the strength of diphtheria antitoxin. A great deal of the knowledge accumulated at that time has a distinct bearing on the interpretation of the phenomena now seen in the cutaneous reaction known as the Schick test.

Soon after the appearance of the reports concerning the clinical value of the intradermal diphtheria toxin test, I became interested in studying the character of the reaction and its behavior under the influence of repeated injections. My interest was held because of the occurrence of happenings analogous to those encountered with repeated injections of horse serum and cowpox vaccine, which had to be explained on entirely different grounds, and also because of the fact, observed so many times in my series of primary injections, that reactions are frequently delayed beyond the usual twenty-four to forty-eight-hour period, to as late as three or four days. Finally, the chief object of my study was to determine if possible, by means of this simple reaction, whether any degree of active immunity could be induced by these infinitesimally small doses of diphtheria toxin.

The enormous change in the biochemic state of the body that is induced by minute amounts of horse serum, egg white, etc., and the well-known peculiar animal racial differences of reaction to injected substances of various kinds seemed to warrant one in devoting some time to this study, even though it had been quite generally admitted that the injection of such small doses of toxin as are represented in 0.1 c.c. of the solution used for the Schick test could have no effect in the production of immunity.

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Toxin Employed and Method of Injection: The two lots of diphtheria toxin use were kindly furnished by Parke, Davis & Co. of Detroit. The L + dose of Lot 1 is 0.18 c.c., of Lot 2, 0.18 c.c. The minimum lethal dose of Lot 2 was estimated to be 0.0015 c.c. Both lots came from the same original supply. The former lot was not so constantly kept on ice as the latter. Except when otherwise specified, Lot 1 may be understood to have been used. The usual fine, sharp needle method of intradermal injection with an all-glass finely graduated tuberculin syringe was used in making the injections, 0.1 c.c. being carefully injected intracutaneously just beneath the epidermis.

PART I

Of eighty-one persons taken at random, ages varying from 2 days to adult life, in whom careful daily observations and measurements were made, fifty reacted positively and thirty-one negatively. These injections were made during the months of November, December, January, February, March and April, 1914 and 1916.

Of the fifty positively reacting cases, the first evidence of a definite reaction was observed on the first day in twenty-one cases; on the second day in thirteen cases; on the third day in eight cases, and on the fourth day in eight cases.

Of these fifty cases, the height of the reaction (the maximum) was reached on the first day in eight cases; on the second day in ten cases; on the third day in twenty cases; on the fourth day in eleven cases, and on the fifth day in one case.

Of the eight reactions showing themselves first on the fourth day, all faded away very quickly, within forty-eight hours of their appearance. Of the twenty-one first-day reactions, twenty faded away very slowly, many showing distinct discoloration beyond the seventh day; and one, Case 56, showing a faint reaction, faded away quickly; but a note made five days after the injection records a "stain"; it was accordingly regarded as a positive case. Reactions appearing on the second and third day, like those appearing on the first day, also disappeared slowly. These cases will be referred to again under the caption "Successive Injections."

The age incidence of reaction of the eighty-one patients is as follows:

	Positive	Negative	Total	Per Cent.
Under 5 months.....	4	13	17	23
5 to 12 months.....	5	1	6	83
1 to 5 years.....	21	3	24	87
6 to 12 years.....	13	12	25	52
Adults	7	2	9	77
	<hr/>	<hr/>	<hr/>	<hr/>
Total	50	31	81	62

Observations on the Effect of Varying Strengths of Diphtheria Toxin.—In a susceptible person distinct, measurable and typical reactions were obtained with toxin dilutions as high as 1 to 50,000. One-tenth c.c. of this solution represents two millionths of a gram, or two thousandths of a milligram of toxin. By reference to Figures 1, 2, 3, 4, 5 and 6, forearm D. O. W., the progress of the reactions of the six different dilutions may be seen. The amount of toxin contained in 0.1 c.c. of these solutions is as follows:

No.	Dilution	Dose, C.c.	Toxin, Gm.
1	1 to 50,000	0.1	0.000002
2	1 to 40,000	0.1	0.0000025
3	1 to 30,000	0.1	0.0000033
4	1 to 20,000	0.1	0.000005
5	1 to 10,000	0.1	0.00001
6	1 to 5,000	0.1	0.00002

The exact measurements and other daily recorded phenomena of the reactions will be found in Table 1. It will be observed that, as one should expect, increasing concentrations of the solutions, namely, the greater the quantity of the toxin, the more vigorous the action of the toxin on the unprotected cutaneous cells, and vice versa, the less the reaction of the body against the toxin. This distinctive effect of the toxin on the upper skin structures can go on up to the point of producing a large blister, Figures 7, 8 and 9, without producing any appreciable harm to the individual aside from the local discomfort which comes in these cases. A series of thirteen tests was made, 0.1 c.c. toxin (L + dose 0.18 c.c.) of a dilution of 1 to 1,000, that is, 0.1 mg. of toxin being used. The reactions are recorded in Table 2. Large vesicle formations (blisters) were observed in five of these cases, namely, 4, 6, 7, 8 and 13.

So much has been written concerning the character of a typical reaction that I shall refer to but a few points here: (1) the interpretation of a two-zone reaction; (2) the character of the periphery of the lesion; (3) the occurrence of scaling or desquamation; (4) the size of the reaction as influenced by the strength of the toxin; and (5) edema.

1. The Two-Zone Reaction: The statement is not infrequently made that a lesion with a dark center surrounded by a lighter pink areola, such as one so commonly sees in second intradermal injections of horse serum, should be looked on with suspicion as an indication of a pseudo or anaphylactic reaction. While doubtless a pseudo or protein reaction may occur with diluted diphtheria toxin, what I have termed a two-zone lesion does very frequently occur as a result of the action of the toxin itself. It is only a matter of either concentration, as is shown in Figures 1 to 6, or of individual tolerance, as is seen with the



Fig. 1.—Twelve hours after injection. This and the five succeeding illustrations show the progress of the reactions of the six different dilutions: 1, 1 to 50,000 dilution toxin; 2, 1 to 40,000; 3, 1 to 30,000; 4, 1 to 20,000; 5, 1 to 10,000; 6, 1 to 5,000. A reading glass will aid greatly in bringing out the detail of the lesions.

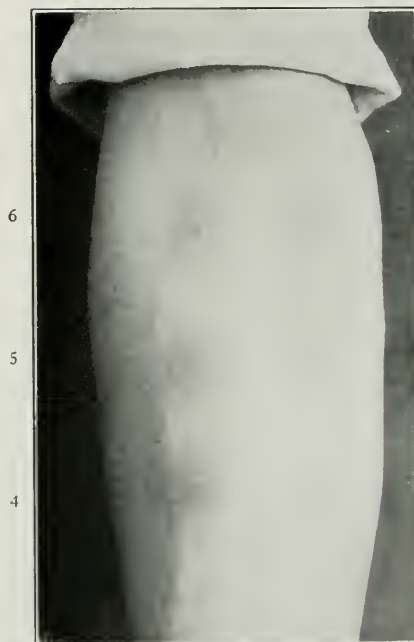


Fig. 2.—Twenty-four hours after injection. Note the slight general swelling. The vein is less visible.



Fig. 3.—Second day. General swelling more marked.



Fig. 4.—Third day. Vein cannot be seen.

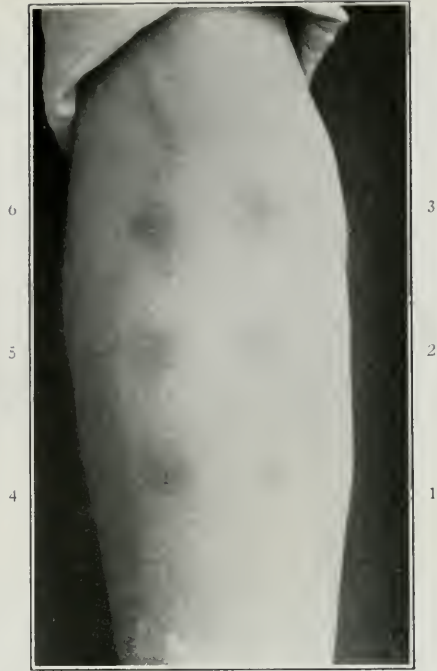


Fig. 5.—Sixth day ; 5 and 6 (see numbers as given in Figure 1) show wrinkling.



Fig. 6.—Eighth day ; 5 and 6 (see numbers as given in Figure 1) desquamating.

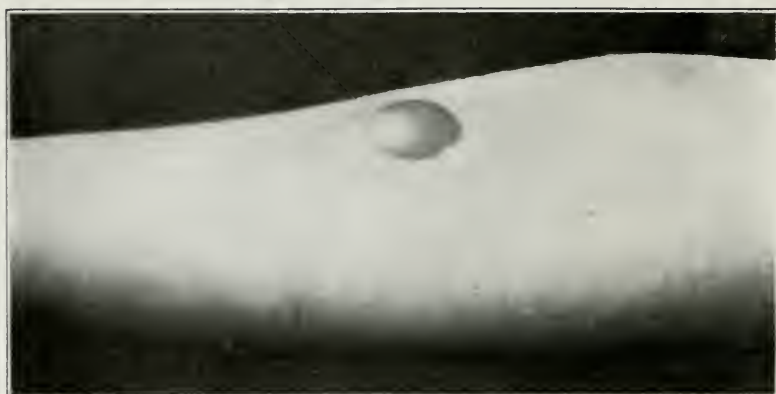


Fig. 7.—Lesion following the intradermal injection of 0.1 c.c. toxin diluted 1 to 1,000.



Fig. 8.—Lesion following the intradermal injection of 0.1 c.c. toxin (L + dose 0.18 c.c.) diluted 1 to 1,000. This and figure 7 illustrate the same case, different views. There are three well-defined zones—the vesicle, the anemic area surrounding it, and the pink areola.



Fig. 9.—Lesion following the intradermal injection of 0.1 c.c. toxin (L + dose 0.18 c.c.) diluted 1 to 1,000.

TABLE 1.—REACTIONS FOLLOWING VARYING STRENGTHS OF DIPHTHERIA TOXIN ADMINISTERED INTRADERMALLY

Date	Time After Injection	Site Number	Description of Reaction
4/12/16	12 hours	1	1 to 50,000. Faint hyperemia 13 × 17,* diffuse, flat
		2	1 to 40,000. Definite hyperemia 17 × 21, definite border, flat
		3	1 to 30,000. Definite hyperemia 15 × 22, pale red, definite border
		4	1 to 20,000. Marked hyperemia 17 × 18, light red, slightly elevated in center
		5	1 to 10,000. Marked hyperemia 20 × 25, red, definite border, slight elevation, pain on pressure
		6	1 to 5,000. Marked hyperemia 22 × 25, center deeper red, 5 × 7, elevated
4/13/16	24 hours	1	15 × 20, diffuse border, flat, pink.
		2	17 × 25, more definite border, flat; more hyperemic than 1
		3	22 × 27, more definite border, slightly more hyperemic than 2
		4	20 × 27, definite border, center slightly elevated, deeper pink, slight tenderness
		5	27 × 35, definite border, elevated slightly, not as much as 4, deeper pink, no tenderness
		6	28 × 35, border indefinite, same color as 5, darker pink zone at center, 5 × 5, slightly tender; slight edema. See Figure 2
4/14/16	2d day	1	10 × 10, pink tint, distinctly fading, flat, margin more definite
		2	15 × 15, pink tint, distinctly fading, flat, margin more definite
		3	15 × 15, pink tint, distinctly fading, flat, margin more definite
		4	15 × 15, pink tint, distinctly fading, deeper pink than 1, 2, 3, flat. Slight wrinkling
		5	20 × 23, deeper pink than 4, definite border, flat, pain on pressure, slight wrinkling
		6	20 × 30, slightly deeper pink than 5, definite border, flat, pain on pressure, slight wrinkling. The whole arm is slightly swollen and there is a slight pinkish hyperemic flush surrounding all the areas measuring 120 × 75
4/15/16	3d day	1	10 × 10, yellowish brown stain, not hyperemic
		2	10 × 15, fading, dull pink, slightly hyperemic, margin more diffuse
		3	10 × 15, fading but brighter than 2, hyperemic, flat, margin more diffuse
		4	15 × 15, fading but brighter than 3, hyperemic, flat, very slight wrinkling
		5	20 × 23, bright red, darker than previous day, hyperemic, flat, no soreness
		6	18 × 30, same as 5, flat. The general hyperemia described for 2d day has gone and the general swelling or edema of the forearm is distinctly less, but still noticeable, the veins are still obliterated
4/16/16	4th day	1	Almost gone, stain, which cannot be measured. The whole diffuse suggestion of discoloration was about 15 × 15
		2	10 × 15, just visible, brownish pink, no definite outline
		3	Seems smaller than 2, cannot measure, fading
		4	Fading, very finely wrinkled, about 15 × 15
		5	20 × 23, still dark pink, faded since 3d day, more dry on surface, wrinkled a little
		6	15 × 25, a little more marked than 5, no scaling, no marked wrinkling, general swelling less, veins still invisible

* Measurements are given in millimeters.

TABLE 1.—REACTIONS FOLLOWING VARYING STRENGTHS OF DIPHTHERIA TOXIN ADMINISTERED INTRADERMALLY—(Continued)

Date	Time After Injection	Site Number	Description of Reaction
4/17/16	5th day	..	All fading markedly
		1	Stain just seen
		2	10 × 15, fainter than 4th day
		3	10 × 10, fading, very diffuse border
		4	Same, a little more wrinkled
		5	Nearly the same, border less defined, wrinkled a little more
		6	Same, 15 × 25, deeper red than others, otherwise same as 5
4/18/16	6th day	..	All very much more faded
		1	2, 3 and 4 cannot be measured
		5	15 × 20
		6	15 × 25
		4	5 and 6 more wrinkled, no scaling yet
4/19/16	7th day	..	All fading much more
		1	Almost invisible
		5	and 6 scaling in large flakes
4/21/16	8th day	1	and 2, no scaling
		3	Faint
		4	5 and 6 marked

standard Schick reaction (0.1 c.c. = 0.5 minimum lethal dose of toxin). This type of reaction is plainly seen in Figure 10. There is distinct edema in the center, and little or none at the periphery; necessarily there will be a difference in the color at these two places. A perfectly uniform color is probably more commonly seen than this two-zone reaction, however; even in some reactions that seem to be faint, careful observation will show not infrequently a darker central area surrounded by a lighter areola.

2. The Margin of the Lesion: The statement is sometimes made that the margin of the lesion must be well defined. This, too, depends largely on the strength of the solution and the susceptibility of the individual. In many of the reactions cited in this report, as well as in the series shown in Figures 1 to 6 and in Table 2, the statement, "diffuse border, the lesion cannot be measured, etc.," will be encountered frequently. We have had previous proof of a positive reaction in some of these individuals, who now react less markedly because of a certain degree of immunity. This diffuse margin is well shown at sites

TABLE 2.—DIPHTHERIA TOXIN 1 TO 1,000 (L + D 0.18 C.c.) 0.1 C.c.
INTRADERMALLY, SEPT. 22, 1915

Case No.	Name	12 Hours	18 Hours	24 Hours	36 Hours	5 Days
1	Mr. B.*	7 × 9,† pale pink	10 × 10, red, elevated, definite border	15 × 15, faint pink, raised, margin red, center 2 × 3	8 × 8, red area, no induration
2	Mr. H.	20 × 20, marked reaction, marked elevation, edema	20 × 25, same as at 12 hours	30 × 35, pale pink area, red center 15 × 15, border indefinite	20 × 20, pink fading	Fading
3	Mr. S. B.	7 × 8, very pale pink, no elevation	10 × 12, red, definite border, elevated	12 × 12, same as at 18 hours	Fading
4	Miss D.	17 × 22, red, elevated, definite border	23 × 25, same tint, border fading	35 × 35, elevated, indurated, border definite	25 × 25, red center, pink area	
5	Miss R.	11 × 12, deep red, definite border, slight elevation	10 × 10, pale pink border indefinite, slight elevation	18 × 28, deep red center 8 × 8, pink area, border definite, all elevated	10 × 10 vesicle area red and edematous	10 × 10, vesicle dry, area about it 5 mm. wide. Total area 15 × 15
6	Miss S.	17 × 22, deep red, marked elevation, border definite	23 × 35, same as at 12 hours	23 × 35, same as at 18 hours	Arm bandaged, definite blister formed	Arm bandaged, definite blister formed
7	Mr. B.	10 × 13, pale pink, diffuse border	17 × 20, pale pink, definite border	20 × 25, pink, fading	Blister 12 × 15, area about it 4 mm. wide, total area 15 × 19
8	Miss F.	18 × 22.....	50 × 70, red center, 20 × 22, area red	Vesicle said to have formed, not seen
9	Mr. O.	20 × 20, center elevated, hyperemia fades at border	40 × 30, pink with bright red center	40 × 30, same as at 18 hours	55 × 80, red, elevated center marked, border pink	10 × 10, pigmented rough area, desquamating
10	Mr. E.	22 × 30, bright red, marked elevation, border definite	28 × 30, same as at 12 hours			
11	Mr. G.	10 × 20, pink, flat, fading margin	30 × 40, slight edema, no vesicle	
12	Mr. Er.	10 × 15, pale pink, flat	14 × 15, pink, slightly elevated, border definite	14 × 15, same, but border less distinct	19 × 20, pink fading, no elevation	Negative
13	Miss S.	18 × 25, deep red, elevated, border definite	20 × 25, same as at 12 hours	30 × 35, bright red, margin raised	30 × 35, pink fading, no edema	Blister 20 × 20, 4 mm. high, area 45 × 60, white anemic band around vesicle 5 mm. wide. See figures 7 and 8

* Patient had 1,000 units of antitoxin subcutaneously.

† Measurements are given in millimeters.

1 and 2, Figure 2. A definite impression of a typical reaction is here gained, but one could not definitely measure the lesion. It is very difficult to get a good photograph of a faint pink lesion. Many photographs of Schick tests show a measureable lesion with a definite border, when in fact beyond the area which seems fairly sharply defined is a gradually diminishing zone which fades almost imperceptibly into the color of the skin.

3. The Occurrence of Scaling: The typical lesion following the injection of 0.1 c.c. of Schick solution into a distinctly susceptible person almost, although not invariably, finishes up with characteristic

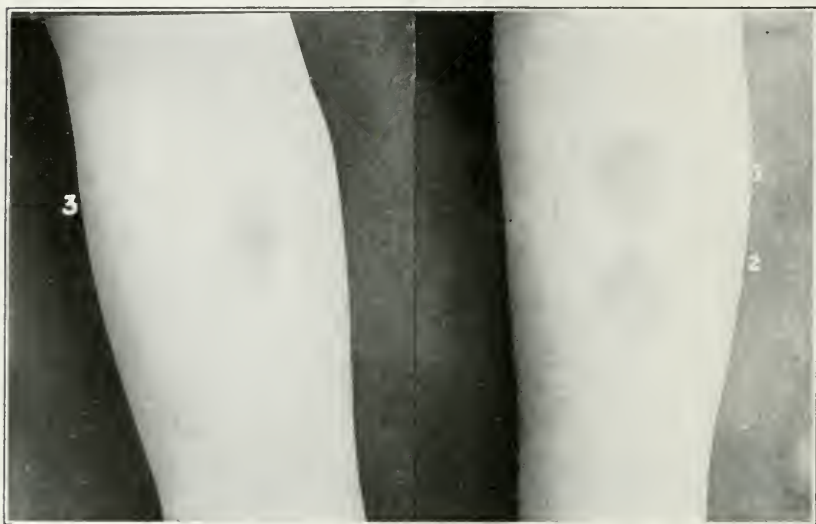


Fig. 10.—Madelain B., photograph taken March 28, 1916, eight days after the first intradermal injection: 1, first intradermal injection of 0.1 c.c., 1 to 20,000 dilution, on March 20; 2, second intradermal injection of 0.1 c.c., dilution 1 to 10,000, March 21; 3, third intradermal injection of 0.1 c.c., dilution 1 to 10,000, March 25. Nos. 1 and 2 are desquamating. Entire lesion elevated 1 mm. above surface, and has a leathery, thickened feeling. Total area at 3 is 18×25 mm., pink, central portion dark pink, slightly elevated, slight edema. The two zones are distinguishable.

scaling or desquamation, Figures 6, 10 and 12. As here shown, the lesion is often elevated well above the level of the skin. In less susceptible persons only a yellowish or brownish yellow stain remains, and this may vanish very quickly. This is well shown in the case recorded in Figure 11. This patient, after a degree of acquired immunity, gave no scaling at the point of the fifth injection. The same result, no scaling, was encountered many times in the series of successive injections.

4. The Size of the Reaction as Influenced by the Strength of the Solution: The average maximum size of lesions produced by different dilutions of the same lot of toxin is given as follows, the measurements being taken from the fifty positive cases in the primary series of eighty-one cases:

Dilutions	No. of Cases	Average Maximum Reaction, Mm.	Amount Toxin, C.c.
1 to 20,000	10	10.9×15.1	0.000005
1 to 10,000	34	15.5×14.6	0.00001
1 to 1,000	13	27.4×34.6	0.0001

The reactions obtained with 1 to 20,000 and 1 to 10,000 solutions are the same, while those with the stronger solutions are very much greater in size.

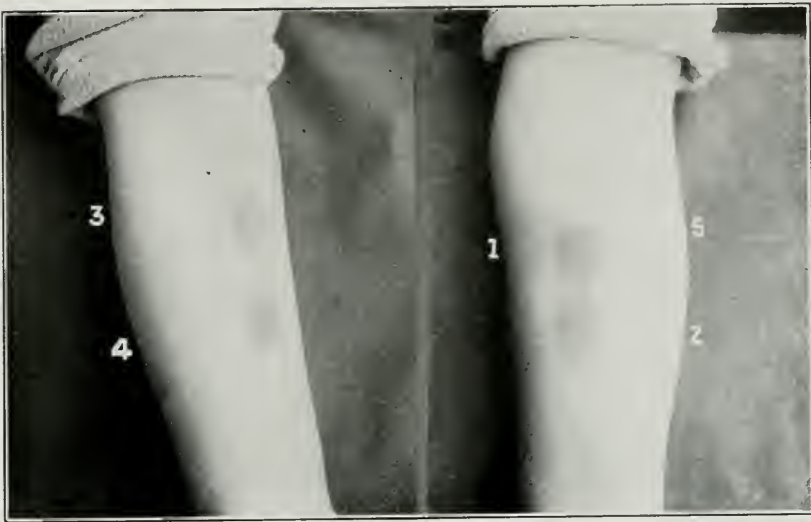


Fig. 11.—Madelain B., received on March 28, 1916, the fourth intradermal injection of 0.1 c.c. of toxin, and on April 11 the fifth injection of the same quantity on the left forearm just to the right of No. 1. The photograph was taken April 13. The age of each lesion on this date was as follows: 1, twenty-nine days; 2, thirty days; 3, nineteen days; 4, sixteen days, and 5, two days. This illustrates the diminishing reaction following successive injections No. 5, while 30×35 mm. was only a faint flush; the day following it was a light brown stain. Observe that lesions 1 and 2 are still very noticeable.

The size of the reaction as influenced by the same dilution of different lots of toxin varies according to the strength of the toxin itself. No two lots of toxin are necessarily the same. On request, Parke, Davis & Co. of Detroit have kindly furnished me with the L + dose of five lots of diphtheria toxin taken at random, to which I add that of the lot used in making these tests, as follows: 0.5 c.c., 0.29 c.c., 0.25 c.c., 0.5 c.c., 0.29 c.c., 0.18 c.c. The L + dose of toxin used by Schick was

0.005 c.c.; accordingly, if one uses a standard-sized needle to deliver a definite amount of toxin into the skin, as has been recently advocated by Dr. Koplik, a definitely standardized toxin should be used. Susceptibility to diphtheria toxin, and consequently to diphtheria, can be recognized by very much more dilute solutions of toxin than are usually employed in making the Schick test.

The size of the reaction may be different with the same lot of toxin the reason for which is hard to explain. For example, Mr. W. was given 0.1 c.c. of a 1 to 10,000 solution of Lot 1 and 0.1 c.c. of Lot 2. The lesion resulting from Lot 1 was very much more vigorous than that resulting from Lot 2, as will be seen in Table 3.

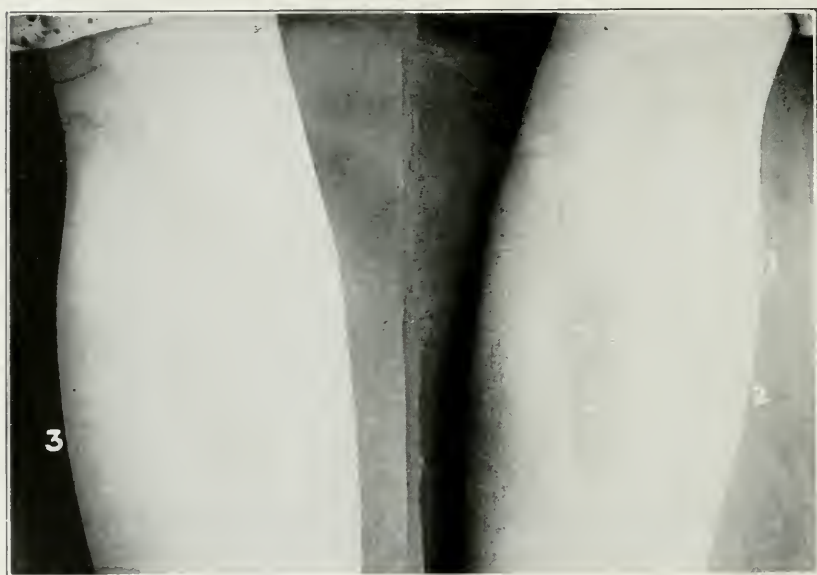


Fig. 12.—Loretta B., photograph taken March 28, 1916, eight days after the first injection, seven days after the second, and three days after the third. The effect of repeated injections is shown. This patient, like the one in Figure 11, continued to react positively after eight injections covering a period of over forty days. The reactions, however, are much modified, more superficial, and fade very much more quickly.

TABLE 3.—VARIATION OF REACTION DUE TO DIFFERENCE IN TOXINS

Toxin Lot	Ten Hours	End of First Day	End of Second Day	End of Third Day
1	+	20 × 20, deep pink, dark center 5 × 5 mm., elevated	10 × 11, deep pink, diffuse border, edema	7 × 8, fading pinkish, can't measure
2	0	15 × 15, fainter, flat	12 × 15, pink, red, flat, border diffuse	9 × 11, deep pink, flat, diffuse

Lot 1 happened to be an old solution, having stood many weeks. We would naturally expect this solution to deteriorate and give a weaker reaction than was obtained with the fresh solution, Lot 2. The solution was perfectly clear, however, and free from visible growth.

5. Edema: The intensity of the reaction, which seems to be indicated by the degree of redness and edema as well as by the size of the lesion, also depends on the strength of solution employed and the susceptibility of the person. In other words, there is no person the intensity of whose lesion cannot be varied at will by the choice of the strength of the solution injected. On the other hand, only those who possess little or no immunity react to the standard Schick solution with marked edema and induration. Such edema, for example, as can easily be seen and felt. Lesser degrees of edema, determined by pressing the lesion with the thin edge of the measuring rule or of the steel tape, are very commonly seen.

Reactions in Infants.—Intradermal tests were made on twenty-three infants, ages varying from 2 days to 10 months (ten positive, thirteen negative, or 56.5 per cent. negative). Negative reactions were encountered very frequently in infants under 5 months. No satisfactory explanation has been given for this immunity. It seems to have been a common clinical observation that young infants are seldom infected with diphtheria. Some authors go so far as to state that diphtheria never attacks an infant in the first half year of life, and believe this is due to a complete immunity. While my short series of cases seems to show that quite a large percentage of infants during this period of life are immune, there is still a large percentage who are not immune. This is rather in accord with the observations of Welch and Schamberg, who state that it has fallen to their "lot to see a large number of infants perish from this scourge (diphtheria) and many of them were under the age of 6 months." In their collection of 9,011 cases, 299, or 33 + per cent. were in infants under 1 year. Some observers, notably Schick, found only 7 per cent. of positively reacting cases in infants under 6 months. Similar results were obtained by Kassowitz and Gröer,¹ who report 10 to 20 per cent. positive. On the other hand, Kleinschmidt² found no antitoxin in sixteen out of eighteen infants examined.

It is sometimes very difficult to determine reactions of moderate degree in the newly born, because of erythema neonatorum, and particularly in some cases of icterus neonatorum, associated with erythema

1. Kassowitz and Gröer: *Jahrb. f. Kinderh.*, 1913, lxxviii, 609.

2. Kleinschmidt: *Jahrb. f. Kinderh.*, 1913, lxxviii, 442.

neonatorum. A very good light and a very careful observation is necessary, while in infants beyond the first two or three weeks of life the lesion is as easy to see as it is in a blond.

Family Reactions.—Park³ and his co-workers have called attention to the interesting point of family reactions; that is, if it is found that one member of a family of children reacts negatively or positively to a Schick test, all the rest of the children react in the same way. This observation has been confirmed by others. An early observation bearing on this point is that of Theobald Smith,⁴ who in 1907 showed that conferred diphtheria immunity was transmitted to the offspring of guinea-pigs. It was further shown that this immunity remained active only over a period of thirty days, after which it gradually decreased until six months, when the offspring were no longer immune. This suggested to me the advisability of testing the mother and infant. The data obtained in this investigation are shown in Table 4.

TABLE 4.—RESULTS OF INTRADERMAL TEST APPLIED TO MOTHER AND CHILD

Number	Mother		Reaction in Infant	Age of Infant, Days
	Name	Reaction, Mm.		
1	West.....	15 × 15	Negative	10
2	Gray.....	20 × 21	Negative	9
3	Haynes.....	+ +20 × 25	Positive, 10 × 15	3
4	Pruun.....	+ +20 × 25	Negative	2
5	Sweet.....	0	0	10
6	Bibbins.....	+ +30 × 30	0	3
7	McClure.....	+ +15 × 20	Positive +	4
8	Calhoun.....	+ +25 × 25	Positive +	6
9	Armstrong.....	+ +20 × 25	Positive ++	4

Table 4 shows that the mother and child were both positive in four instances, both negative in one instance, and mother positive and child negative in four instances. From these data it will be seen that while mother and child usually react in the same way, the infant may frequently give a negative reaction and the mother a positive. Kassowitz and Gröer believe the antitoxin is derived from the mother. The observations made above would lead one to believe that there are probably factors other than transmitted immunity entering into the negative reaction of the new born.

3. Park, Zingher and Serota: Arch. Pediat., 1914, p. 484.

4. Smith, Theobald: Jour. Med. Research, 1907, xi, 359.

Influence of Time of Year on the Reaction.—It is a well-known clinical fact that diphtheria is more prevalent during certain seasons of the year. The U. S. Mortality Report for 1900, for example, records 16,368 deaths from diphtheria. Of these, 13,848 occurred during the cool and cold months, while 2,520, or about 15 per cent., occurred during the warm months, June, July and August. The influence of season on susceptibility of animals to diphtheria is well known, and has been recorded by Brown.⁵ The guinea-pigs used in their experiments were more susceptible to diphtheria toxin mixtures in winter than in summer.

A great many toxin Schick reactions have been recorded in the literature, but, unfortunately, the time of year at which these reactions were made is frequently not given. One may infer, however, from the date of publication and from the context the time of year at which the test was made. The cases recorded in Table 5 are, I believe, trustworthy as to season. The figures are only suggestive. It is not at all improbable, however, that it will be found that more negative reactions will be encountered in the warm summer months than in winter.

TABLE 5.—INFLUENCE OF SEASON ON SUSCEPTIBILITY TO DIPHTHERIA AS RECOGNIZED BY THE SCHICK TEST

Age	No. Cases	Summer			No. Cases	Winter			Reporter
		Pos.	Neg.	Per Cent. Pos.		Pos.	Neg.	Per Cent. Pos.	
Under 1 year...	20	6	14	30*	48	16	32	33.3	Moffett and Conrad* Moody† Author
One year.....	27	9	18	33.3*	36	20	16	55.5	
One to 5 years.	24	21	3	87.5	
Totals.....	47	15	32	31	131	66	65	58	

* Moffett and Conrad: Jour. Am. Med. Assn., lxx, 1010.

† Moody: Jour. Am. Med. Assn., lxxiv, 1206.

PART II

SUCCESSIVE INJECTION SERIES

Of thirty-four positive cases in which successive intradermal injections of toxin were given (Table 6) at intervals of five, twelve and seven days, respectively, the time of the reaction was unchanged in nine cases, hastened in twenty cases, delayed in no instance, and completely suppressed in five instances. The character of the reaction was unchanged in five cases, diminished in twenty-four cases, and suppressed in five cases.

5. Brown: Jour. Med. Research, 1912-1913, xxii, 447.

TABLE 6.—SUCCESSIVE EXTRADERMAL INJECTIONS IN POSITIVE CASES

Case Number	1st Injection, Dilution 1 to 10,000			2d Injection, 5 Days after 1st, Dilution 1 to 10,000			3d Injection, 17 Days after 1st, Dilution 1 to 5,000			4th Injection, 29 Days after 1st, Dilution 1 to 10,000			5th Injection, 36 Days after 1st, Dilution 1 to 20,000			On Character of Reaction, Size, Intensity, etc.
	Maxi- mum Reaction, Mm.	Day 1st Reac- tion	Day 1st Reac- tion	Maxi- mum Reaction, Mm.	Day 1st Reac- tion	Day 1st Reac- tion	Maxi- mum Reaction, Mm.	Day 1st Reac- tion	Day 1st Reac- tion	Maxi- mum Reaction, Mm.	Day 1st Reac- tion	Day 1st Reac- tion	Maxi- mum Reaction, Mm.	Day 1st Reac- tion	Day 1st Reac- tion	
1	+	2	2	+	2	Unchanged
2*	7 × 7	3	1	8 × 10	1	8 × 8	2	10 × 17	1	6 × 7	1	Diminished
3*	15 × 22	3	1	4 × 5	1	10 × 17	1	Diminished
7*	10 × 15 ²	1	1	13 × 18 ²	1	12 × 15 ²	1	10 × 15	2	8 × 10	1	Diminished
9*	15 × 17	1	3	15 × 15 ¹	3	6 × 8	2	±	1	7 × 8	1	Diminished
11*	8 × 10	4	2	±	2	Diminished
16	10 × 20	3	1	3 × 7	1	Diminished
17	12 × 12 ²	2	1	20 × 20 ²	1	Diminished
18	15 × 15 ²	2	1	7 × 10	1	9 × 6 ²	1	5 × 5	1	7 × 10	1	Diminished
19	10 × 10 ²	1	1	8 × 10	1	12 × 17 ¹	1	6 × 8	1	10 × 12 ²	1	Diminished
20	7 × 10 ²	3	0	0	0	Suppressed
21	8 × 10	2	2	10 × 14 ¹	2	7 × 7	1	6 × 9	1	12 × 12	1	Diminished
22	10 × 13	1	1	5 × 3	1	5 × 6	1	5 × 8	1	Diminished
23	8 × 8	3	1	11 × 11 ²	1	8 × 10	1	Unchanged

24	10×12	3	15×15	3	7×7	1	8×10	1	Hastened	Diminished
25	\pm	1	1×4^1	1	Hastened	Unchanged
26	15×15	1	5×5^2	1	10×13	1	12×12	1	Unchanged	Diminished
27	18×20^1	2	8×15^3	1	8×10^2	1	8×12	1	8×10	1	Hastened	Diminished
28	12×15^1	2	2×2	1	Hastened	Diminished
29	17×20^2	2	\pm	1	Unchanged	Diminished
30	10×18^3	1	10×10^3	27	8×7^2	1	Unchanged	Diminished
32	12×15	3	\pm	1	Hastened	Diminished
33	8×10	4	\pm	2	Hastened	Diminished
36	\pm	1	0	0	Suppressed	Suppressed
39	10×15	1	10×10	3	Hastened	Unchanged
45	12×20^3	2	16×20	2	5×7	1	Hastened	Diminished
46	18×22	2	19×20	27	16×17	2	Unchanged	Diminished
52	15×20^2	1	8×8^1	1	Unchanged	Diminished
53	12×15^3	2	10×10^4	27	10×17^2	1	8×5	1	8×10	1	Hastened	Diminished
54	3×3^3	3	0	0	Suppressed	Suppressed
56	\pm	1	0	Suppressed	Suppressed
57	5×8	1	\pm	2	Hastened	Diminished
59	5×8	1	0	0	Suppressed	Suppressed
61	10×12^3	2	10×10	2	10×13	17	Hastened	Unchanged

* The patients in Cases 1, 2, 3, 7, 9 and 11 received for the first injection a dilution of 1 to 20,000.

† In the maximum reaction column the exponent indicates the day on which the maximum reaction occurred.

Suppressed Reactions.—The suppressed reactions seem to have been brought about definitely by the repeated injection of toxin. All of these cases gave small but nevertheless distinct primary reactions. In two cases the primary reactions were delayed. The suppression was induced by the first injection of toxin.

The Hastened Reactions.—Of the twenty cases in which the time of the appearance of the reaction was hastened by successive injections of toxin, a primary reaction occurred on the second day in eight cases, on the third day in six cases, on the fourth day in six cases.

Of the eight cases reacting on the second day, the hastening of the time of the reaction was effected by the first injection in four cases, by the second injection in four cases.

Of the six cases reacting on the third day, the hastening of the time of the reaction was effected by the first injection in five cases, by the second injection in one case.

Of the six cases reacting on the fourth day, the hastening of the time of the reaction was effected on the first day in four cases, on the second day in one case.

From this observation it seems that the hastening of the time of the reaction is usually effected by the first injection, that is, a delayed primary reaction case through the influence of the first injection responds more quickly to a second injection after an interval of five days.

While analogous to the phenomena seen after second injections of horse serum, this change in reactivity is not an anaphylactic affair. It is in all probability due to an acquired immunity.

The Diminishing Reactions.—Twenty-four of the positively reacting cases showed a diminution in the size and the intensity of the reaction. This was very noticeable in twelve cases (Cases 3, 9, 11, 16, 22, 28, 29, 30, 32, 33, 45, 52, Table 6). The time of the first appearance of the reaction was hastened in sixteen of these cases, unchanged in eight, but in the latter, seven reacted primarily on the first day. In those cases in which the primary reaction occurred on the fourth day the reaction was so slight after the second injection (which was given five days later) as to be marked "+—" in two (Cases 11, 57, Table 6), and "+" in 1 (Case 33). In other words, it was a question whether there was a reaction at all in two cases, with the benefit of the doubt given to the positive side.

The successive changes which occur in the diminishing group of reactions will be appreciated better by referring to Tables 7 to 11, which give the daily measurements, etc. These tables are self-explanatory.

TABLE 7.—CASE 9, CLARENCE Y., AGE 11 YEARS*

Inj. No.	Date of Injection	Dilution of Toxin	Reaction in Mm.						
			1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day
1	11/ 7/14	1 to 10,000	9	0	0	15 × 17, red	15 × 17, fading	Fading	Fading
2	11/12/14	1 to 10,000	0	0	±	15 × 18, faint	Fading	Fading	Fading
3	11/24/14	1 to 5,000	+ ?	6 × 8	..	Fading	Fading	Fading	Fading
4	12/ 6/14	1 to 10,000	±	Fading	0	0	0	0	0
5	12/12/14	1 to 10,000	7 × 8	Fading	0	0	0	0	0

* This case illustrates the hastened and diminishing reaction.

TABLE 8.—CASE 18, BABY W.

Inj. No.	Date of Injection	Dilution of Toxin	Reaction in Mm.						
			1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day
1	11/ 7/14	1 to 10,000	?	++	++	12 × 12	15 × 15,	Fading	Fading
2	11/12/14	1 to 10,000	7 × 10	+ papule	+	+	Fading	Fading	Fading
3	11/24/14	1 to 5,000	5 × 7, bright red	6 × 9	Fading	Fading	Fading	
4	12/ 6/14	1 to 10,000	5 × 5	8 × 8, stain	0	0	0		
5	12/12/14	1 to 20,000	7 × 10	Fading quickly	Stain	—	—		

TABLE 9.—CASE 22, BABY R.

Inj. No.	Date of Injection	Dilution of Toxin	Reaction in Mm.						
			1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day
1	11/ 7/14	1 to 10,000	10 × 13	10 × 12, red	8 × 9, fading	Fading	Fading	Fading	Fading
2	11/12/14	1 to 10,000	5 × 3	+	+	Stain	Fading	0	
3	11/24/14	1 to 5,000	5 × 7	8 × 8	Left hospital			
4	12/ 6/14	1 to 10,000	5 × 6	5 × 6	0	0	0	Returned to hosp.	
5	12/12/14	1 to 20,000	5 × 8	Fading	0	0	0		

TABLE 10.—CASE 45, GENEVIEVE H.

Inj. No.	Date of Injection	Dilution of Toxin	Reaction in Mm.						
			1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day
1	11/ 7/14	1 to 10,000	0	+	12 × 20	Fading	Fading	Fading	Fading
2	11/12/14	1 to 10,000	16 × 20	16 × 20	17 × 20, fading, general rash*	Fading	Fading	Fading
3	11/24/14	1 to 5,000	5 × 7, faint	8 × 8 ?, faint	Left hosp.				

* On Nov. 16, 1914, nine days after the first injection and four days after the second, the patient broke out with a general erythematous eruption, macular in character. This was most noticeable on the right side of the face, where there was a map-like area 7 by 7 cm. There were several large areas on the chest and abdomen 5 by 5 cm. and a few on the arms 2 by 2 cm. The color was deep red. The lips and the lower eyelids were swollen. The cervical glands on the left side were enlarged, but no previous note had been made of their condition prior to injection.

TABLE 11.—CASE 30, ZENA B.

Inj. No.	Date of Injection	Dilution of Toxin	Reaction in Mm.						
			1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day
1	11/ 7/14	1 to 10,000	6 × 13	±	10 × 18	12 × 18	Fading, yellow	Yellow	Fading
2	11/12/14	1 to 10,000	8 × 8	+ not measured	10 × 16, fading	Fading	Fading	Fading
3	11/24/14	1 to 5,000	6 × 7	7 × 8, faint	+ not measured	Fading	Fading	Fading	

The question of delayed appearance of primary reactions referred to in the first part of this report seems to be of some significance. In quite a number of the suppressed and diminishing reaction cases the change consequent on repeated injections of toxin to negative or slight reactions is quite noticeable in the late primary cases. From this, one might infer that individuals reacting to a primary injection of diphtheria toxin on the first day have less immunity than those reacting on the third and fourth day. In other words, a delayed reaction means that the individual has a certain amount of immunity, and will, in all probability, be a case which would more readily become immunized by injection of toxin or toxin-antitoxin mixtures.

The Unchanged Reactions.—Those cases in which the character of the reaction was unchanged are four in number (Cases 1, 23, 25 and 61, Table 6). Two of these cases (1 and 25) were of slight reaction, and the patients passed from under observation after the second injection. The other two (23 and 61) were apparently uninfluenced by repeated injections. In Case 23 the patient missed the third and fourth injec-

tions, thus leaving a period of thirty days between injections. This case, however, showed reaction within the first twenty-four hours, while the reaction did not appear until the third day after the first injection.

Negatively Reacting Cases.—Of the patients reacting negatively to successive injections of diphtheria toxin, sixteen remained in the hospital long enough for a second and third injection, given at intervals of five, twelve and fourteen days. Fourteen of these remained negative, while two gave slightly positive reactions after the second injection. These must be considered variants. Case 58 may have been positive after the primary injection, we marked it "—?," while Case 15, on the other hand, followed the usual distinctly negative course. The reactions were carefully watched over periods of from five to seven days.

This negative group, together with the diminishing positive group, confirms the opinion that toxin even in these minute amounts tends to stimulate the formation of antitoxin, rather than to use up to any appreciable degree the natural antibodies of the organism.

To carry the investigation a little farther, three children with marked reactions to a 1 to 10,000 solution of toxin were selected, an intradermal injection of the same amount of toxin being given at the intervals of one, four, three, fourteen, fifteen, ten and three days, covering a period of forty days. On one day, April 11, 1916, at the time of the fifth injection, 0.2 c.c. of this solution was also injected into the thigh of each child as a control. The noticeable thing about these reactions is that although the children do not react negatively after the repeated injections, the lesion has been definitely modified. Though it has not become smaller, its duration is much shorter, and in a few days after an injection of toxin, the fourth or fifth day, the stain is the same or less noticeable than it is in the first or second lesion. It is a well-known fact in the manufacture of diphtheria toxin that horses develop a very high-grade local immunity in the tissues surrounding the point of injection of the toxin, and a low-grade general immunity.⁶ This is shown by the development of well-marked local necrosis when the same dose of toxin is injected into a remote part of the skin. To guard against this having any influence on the reactions recorded, the injections were made into both arms, and test injections were made into other parts of the skin, such as the thigh, for a control. The changes that have been induced by the successive injections, I believe, are not due to a local skin change. The total amount of toxin used in each of the last three cases was 0.0001 c.c. (minimum lethal dose 0.0015).

6. Smith and Brown: Jour. Med. Research, 1910, xviii, 443.

It has been shown that repeated doses of diphtheria toxin induce immunity in guinea-pigs, but that such immunity does not compare with that induced by toxin-antitoxin mixtures. When toxin alone was used, doses of toxin which were not large enough to produce skin lesions (necrosis and ulceration) were selected. The first doses (Brown⁷) used produced only slight scaling of the skin and little loss of hair. The offspring from such treated mothers showed a resistance to toxin above normal. Amounts of toxin varying from 0.0023 to 0.0098 c.c. (minimum lethal dose 0.007) were injected. Immunity was developed to the point that no local or constitutional reaction was produced by 0.005 c.c. of the toxin. With children, solutions of greater than 1 to 5,000 concentration of our toxin brought about ugly lesions when injected intracutaneously.

The Occurrence of Rashes Following Intradermal Injections of Diphtheria Toxin.—Rashes were observed in five cases, Ula S., Baby G., Genevieve H., Sarah S. and Loretta B. All of these rashes developed after the second injection, and all appeared on the second or third day after this injection was given. These rashes were erythema in four and urticaria in two. That the rashes were due to repeated injection of toxin is well seen in the cases of Loretta B. and Sarah S. In Loretta B. marked erythematous and urticarial patches appeared on the face, 10 by 25 mm., and on the back, 20 by 30 mm., on three different occasions, always the beginning of the second day after an injection. In Sarah S. the urticaria was very marked, extending over the entire body, and persisting for several days. This occurred on two occasions. Cases showing erythema resembled that shown in Genevieve H., but they were not so marked. Genevieve H. developed a macular erythema, beginning the night of the second day following her second intradermal injection, nine days after her first injection. The eruption extended over the entire body, and was most noticeable on the right side of the face, where a large map-like area, 7 by 7 cm. developed. Several large areas developed on the abdomen, 5 by 5 cm., and several on the arms, measuring 2 by 2 cm. The color was a deep red, and the lips and the lower eyelids were swollen. The posterior cervical glands were enlarged on the left side, but no record of their previous condition had been made. These children had never had similar rashes before.

SUMMARY

It would seem from the foregoing observations that the following conclusions are justified:

7. Brown: Jour. Med. Research, 1912-1913, xxii, 445.

1. Successive intradermal injections of very dilute solutions of diphtheria toxin (0.00001 c.c. L. + dose), when given at intervals varying from five to twelve days, provoke the formation of antibodies, and in those cases already exhibiting a certain degree of immunity, bring about a definite immunity as recognized by the intradermal test.

2. An opinion of the degree of natural immunity may be obtained from the time of first appearance and from the character of the primary intradermal reaction. An early primary reaction of ordinary degree indicates absence, or low degree, of immunity. A late appearing primary reaction indicates that such a person has a greater degree of immunity than one who reacts early.

3. The development of immunity induced by means of infinitesimally small successive doses of diphtheria toxin may be recognized by a hastening in the time of the appearance of the reaction, and a diminishing of the size of the lesion.

4. In those cases in which the size and intensity of the reaction was reduced by successive injections of toxin, the time of the appearance of the reaction was hastened in the large majority of cases observed. The greatest change toward a negative reaction occurred in those cases which gave a primary reaction on the third and fourth day.

5. A primary reacting case which does not change its character after a second, third or fourth intradermal injection may be considered one without any reacting bodies, and, necessarily, one in which diphtheria would be easily induced.

6. The degree of immunity induced by such small doses of toxin as are represented by 0.1 c.c. of highly diluted diphtheria toxin, seems to be very slight, and cannot be compared with the results obtained by the use of toxin-antitoxin mixtures. Solutions carrying sufficient toxin to induce immunity when given intradermally are not well borne by the patient.

I wish to acknowledge the kind assistance of Dr. A. H. Beifeld in confirming many of the measurements and observations made.

THE EPIDEMIOLOGY OF PERTUSSIS

INTRODUCTORY *

PAUL LUTTINGER, M.D.

NEW YORK

When a group of workers in the Bureau of Laboratories began in 1913 the study of pertussis, we were confronted with an almost complete lack of data bearing on the epidemiology of the disease in New York City.

It was essential, however, for our investigations, especially for the clinical side, that we gather a certain number of facts on the epidemiology of whooping cough, so that we might be in a position to compare the different methods of treatment and obtain a firm basis for our future clinical conclusions and sanitary recommendations.

Early in the fall of 1913, therefore, I began a preliminary survey, which was continued during the spring of 1914 and subsequently extended so as to cover every season of the year and so planned that quite a complete picture of the whooping cough situation for the last three years was obtained.

The material of these surveys is so extensive, however, that it could not be compressed into one article even by eliminating many charts and tables. Hence, it was decided to limit the present communication to the discussion of purely epidemiologic figures in New York, leaving out comparative studies with other cities, the remaining data to be collected in a future article on the symptomatology of the disease.

The present study will be limited to the discussion of the following sub-headings:

Number of cases investigated.

Incidence of pertussis.

The factor of age in pertussis.

The factor of sex in pertussis.

The factor of seasonal variations in pertussis.

The factor of surroundings in pertussis.

Mortality in pertussis.

Sources of infection—carriers—immunity.

Influence of specific vaccines on pertussis epidemiology.

Conclusions and recommendations.

* Submitted for publication May 22, 1916.

* From the Bureau of Laboratories, Department of Health, New York City.

NUMBER OF CASES INVESTIGATED

The number of cases seen in connection with this study exceeds ten thousand as follows:

Preliminary investigation (1913-1914).....	200
Second Survey (Spring and Summer 1914).....	1,430
Third Survey (Fall and Winter 1915-1916).....	4,200
Hospitals and Institutions.....	1,900
Whooping Cough Clinic (Aug. 4, 1914-Feb. 1, 1916).....	2,600
Private patients and in consultation.....	182
Total	10,512

Not all of the cases were available for deduction and analysis for each of the principal factors in the epidemiology of pertussis; hence, the exact number of cases investigated will be given when these separate factors are discussed.

INCIDENCE OF PERTUSSIS

Owing to the fact that pertussis has been a reportable disease only since 1900, it is extremely difficult from official records to arrive at any conclusion as to its incidence. Thus, during the years 1900 to 1903 there were more deaths from pertussis in Manhattan and Bronx than cases of whooping cough reported in the whole city of New York, as may be seen from the following figures:

CASES AND DEATHS FROM PERTUSSIS 1900-1902

Year	Greater New York, Cases Reported	Manhattan and Bronx, Deaths from Pertussis
1900.....	174	318
1901.....	114	159
1902.....	348	385

There is no reason why all cases of whooping cough coming to the attention of physicians should not be reported. Placarding, which is the usual deterrent in the reporting of other infectious diseases, is not enforced in cases of pertussis. Continued agitation by educating the private practitioner and keeping the subject before the profession does seem to increase the number of reported cases. This is evident from the number of cases reported during the last three years when pertussis had been discussed in the medical press more extensively than before.

CASES REPORTED FROM 1913-1915 IN THE CITY OF NEW YORK

Year	No. Cases
1913.....	3,529
1914.....	3,798
1915.....	6,868

Of course there will always remain an appreciable number of cases which will not be reported, simply because no physician will be called to attend them. This number also could be reduced to a minimum by public health education, which would constantly point out the danger of neglecting the disease and the necessity of early medical care.

Another error which must be eliminated before the official reports would reflect the actual incidence of pertussis in New York City is due to the comparatively large number of cases which are often reported as whooping cough, when they really are simple colds or nonspecific bronchitis. Such cases are more apt to be reported from school lists and could be easily avoided by reporting as true cases only such as show a paroxysmal cough with vomiting or a whoop; all others should be revisited before being definitely reported.

During our preliminary survey we found only 161 true cases of whooping cough out of 200 cases reported as such. Curiously enough, two cases of mumps were reported as pertussis, the reporter being under the impression that pertussis was the latin name for mumps.

That private practitioners were not the only offenders in failing to report their whooping cough cases was brought out by Billings¹ in 1910, who found that forty-nine out of 116 institutions did not report whooping cough cases and that in only fourteen were new applicants examined before assignment to their respective classes.

In order to ascertain the ratio of unreported cases of whooping cough to those reported, I undertook a short investigation during the last three weeks in November, 1914.

First, tenement houses were visited from which cases of pertussis had been reported, with the following results:

District	No. Tenements Visited	Cases Reported	Cases Not Reported
Downtown	19	21	48
Yorkville	14	20	30
Harlem	20	28	61
Bronx	3	8	10
Total	56	77	149

Then houses were visited contingent to those from which cases had been reported. The figures obtained were as follows:

District	No. Tenements Visited	Cases Reported	Cases Not Reported
Harlem	10	0	42
Bronx	2	0	3
Total	12	0	45

1. Billings: The Administrative Control of Whooping Cough, Dept. of Health Reprint, Series 1914.

Finally, some houses were visited at random, the results being tabulated as follows:

District	No. Tenements Visited	Cases Reported	Cases Not Reported
Yorkville	3	0	1
Harlem	14	0	16
Bronx	10	0	0
Total	27	0	17

Thus, in ninety-five houses visited there had occurred during the months of August, September, October and part of November, 1914, 288 cases of pertussis of which only seventy-seven, or 26.7 per cent. had been reported. Twelve of the seventy-seven cases, furthermore, were apparently plain coughs, which further decreased the percentage of true cases of whooping cough reported.

Since this investigation, we have collected figures which would indicate that probably only 15 per cent., and by counting adult cases and those of an abortive type, presumably only 10 per cent. of the pertussis cases occurring in New York City are reported.

Under these circumstances the case mortality rate of whooping cough should be revised as soon as more reliable figures are obtained through the reporting of a larger number of cases, although one could not expect the case mortality to become absolutely accurate.

THE FACTOR OF AGE IN PERTUSSIS

The real significance of pertussis as a mortality factor becomes apparent when we study the age of the children who are affected by the disease and who succumb to it. Unfortunately, the department publications do not show any age incidence. We had to draw on our own material.

Thus, of 10,000 cases of pertussis which we analyzed in regard to the age we obtained the following tabulation:

INCIDENCE OF PERTUSSIS ACCORDING TO AGE		
Ages	No. Cases	Percentage
Under 1 year.....	1,940	19.4
1 year, under 2.....	2,019	20.1
2 years, under 5.....	4,010	40.1
5 years, under 15.....	1,799	17.9
15 years and over.....	232	2.3

It will thus be seen that 80 per cent. of all patients with pertussis were under 5 years of age. At the Whooping Cough Clinic we obtained somewhat similar figures. Among over 2,000 true cases of pertussis, we found the following proportion:

Age	Percentage
Under 1 year.....	24.3
1 year, under 2.....	20.8
2 years, under 5.....	38.6
5 years, under 15.....	15.1
15 years and over.....	1.2

TABLE 1.—DEATHS FROM PERTUSSIS IN FORMER CITY OF NEW YORK FROM 1866 TO 1915, ACCORDING TO AGE GROUPS AND SEX

Year	Total Deaths	Male	Female	Under 1 Year		1 Year and Under 2		2 Years and Under 5		5 Years and Under 15		15 Years and Under 25		25 Years and Under 45		45 Years and Under 65		65 Years and Over	
		Male	Female	Male	Fe- male	Male	Fe- male	Male	Fe- male	Male	Fe- male	Male	Fe- male	Male	Fe- male	Male	Fe- male	Male	Fe- male
1866	114	48	66	23	27	16	22	8	15	1	2								
1867	155	65	90	39	45	18	26	8	16	..	3								
1868	217	89	128	53	64	27	43	8	18	1	3								
1869	338	152	206	74	98	46	63	26	39	6	6								
1870	201	79	122	44	61	16	38	18	22	1	1								
1871	465	196	269	103	136	65	78	26	49	2	6								
1872	565	261	304	135	143	66	75	50	72	10	14								
1873	298	117	151	56	79	29	41	31	29	1	1	1	..	1	..
1874	489	214	275	110	151	58	69	45	49	1	4	1	..	1	..
1875	407	185	222	114	123	50	55	19	40	2	4								
1876	406	178	228	97	113	40	59	35	49	5	6	..	1						
1877	440	180	251	98	112	47	75	39	53	5	11			1					
1878	382	159	223	86	113	37	63	33	42	3	4	1	..	1	..
1879	537	253	284	128	132	69	87	49	55	7	10								
1880	277	134	143	64	60	38	53	30	26	2	4								
1881	286	135	151	73	63	33	54	23	30	6	4								
1882	638	289	369	155	187	80	90	46	78	8	13	..	1						
1883	327	169	158	80	88	45	37	35	28	8	3	1	1	1	..	1	..
1884	490	226	264	131	139	56	68	30	50	9	7								
1885	439	216	279	118	127	57	81	39	62	2	9								
1886	575	261	314	144	159	70	88	40	57	7	10								
1887	188	87	101	49	48	23	30	13	18	2	4	1	..	1	..
1888	573	238	335	119	163	58	89	47	65	14	17	1	..	1	..

[illegible]

The tabulation shows that nearly 84 per cent. of all pertussis patients were under 5 years of age. These figures prove conclusively that the majority of children who are liable to contract pertussis are under 5 years of age and that 50 per cent. of these are between the ages of 2 and 5.

The deaths according to age for the last fifty years in the former city of New York aggregate the sum of 17,046 (Table 1), distributed as follows:

DEATHS ACCORDING TO AGE FOR THE LAST FIFTY YEARS IN THE OLD CITY OF
NEW YORK (MANHATTAN AND BRONX)

Under 1 year.....	8,668	50.8
1 year, under 2.....	4,659	27.3
2 years, under 5.....	3,213	18.8
5 years, under 15.....	471	2.7
15 years, under 25.....	13	0.3
25 years, under 45.....	10	
45 years, under 65.....	8	
65 years and over.....	4	
Total	17,046	

This tabulation shows that 97 per cent. of all deaths occurred in patients under 5 years of age, and that over 50 per cent. of all deaths occur in children under 1 year of age. We have seen that the incidence of the disease is about 20 per cent. in that age, which means that while the danger of contracting the disease is relatively slight for children under 1 year of age, the danger of dying from the disease is the highest.

Children of 2 years and under 5, on the other hand, are most liable to become infected, but have the lowest mortality in the group of children under 5 years of age.

Children over 5 and under 15, whose liability of infection is less than those under 1 year, or those of one year and under 2, show a very low percentage (less than 3 per cent.), while all adults show a negligible percentage of deaths (0.3 per cent.), although the rate of incidence, which seems to be only about 2 per cent., is very important when one remembers their rôle of carriers and the tendency of the disease to run an atypical course and hence remain undetected and unreported.

The age ratio is fairly constant and can be ascertained by analyzing any group of cases. The number of deaths, for instance, in the city of New York during 1915 was 385, as may be seen from Table 2, the proportion being as follows: Under 1 year, 52.2 per cent.; 1 year and under 2 years, 30.3 per cent.; 2 years and under 5 years, 14.2 per cent.; total below 5 years, 96.8 per cent.

Figure 1 illustrates the factor of age in pertussis, both as to the incidence and deaths, the former based on 10,000 cases and the latter on over 17,000 deaths.

THE FACTOR OF SEX IN PERTUSSIS

The factor of sex in pertussis is even more remarkable and constant than the factor of age. No matter what set of figures we analyze, we are struck with the high incidence and mortality among girls. In fact, after carefully going over the figures of other diseases I can state unreservedly that it is the only infectious disease attacking both sexes which shows a marked and constant preponderance of deaths and inci-

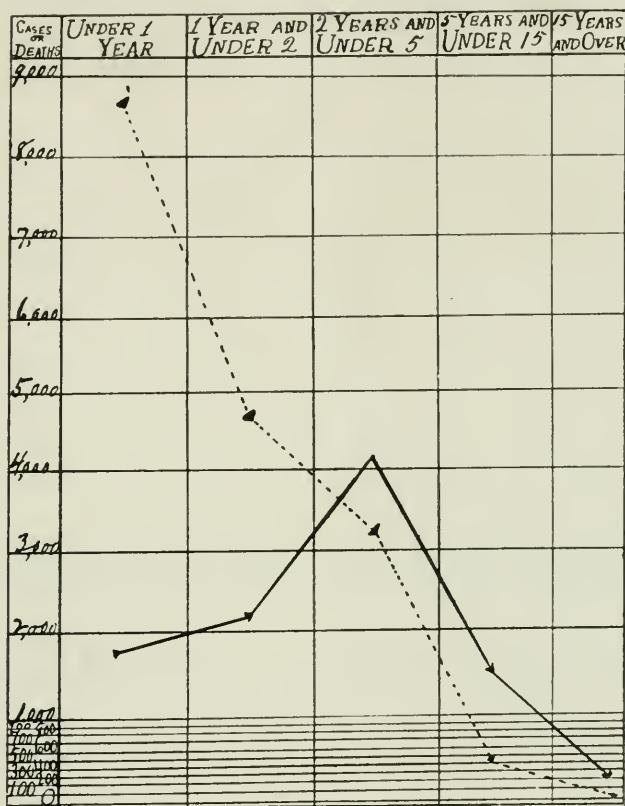


Fig. 1.—Comparative curves of the incidence and mortality of pertussis according to age, based on 10,000 and 17,046 cases, respectively.

dence among girls. This increased severity in girls is probably to be ascribed to anatomical differences in the construction of the larynx and possibly to greater susceptibility of the nervous system of the girl.

The number of cases reported to me from Manhattan and the Bronx from Aug. 4, 1914, to Aug. 4, 1915, amount to 2,711. Of these, 1,180 were among boys (43.5 per cent.) and 1,477 were among girls (54.4 per cent.). The sex of fifty-four (2.1 per cent.) was not reported.

TABLE 2.—DEATHS FROM PERTUSSIS IN GREATER NEW YORK IN 1915,
ACCORDING TO WEEKS, SEX AND AGE GROUPS

Week Ending	Total Deaths	Male	Female	Under 1 Year*	1 Year and Under 2	2 Years and Under 5	Total Deaths Under 5	Over 5 and Under 15
January 2.....	2	..	2	1	..	1	2	..
9.....	1	1	1	..	1	..
16.....	4	1	3	1	2	1	4	..
23.....	5	4	1	3	1	1	5	..
30.....	2	1	1	..	1	1	2	..
February 6.....	4	2	2	4	4	..
13.....	3	1	2	2	1	..	3	..
20.....	3	1	2	1	2	..	3	..
27.....	6	5	1	5	1	..	6	..
March 6.....	6	5	1	5	1	..	6	..
13.....	4	..	4	3	1	..	4	..
20.....	3	1	2	1	2	..	3	..
27.....	3	..	3	2	1	..	3	..
April 3.....	6	2	4	4	1	1	6	..
10.....	11	3	8	5	2	4	11	..
17.....	15	9	6	8	4	2	14	1
24.....	10	3	7	5	5	..	10	..
May 1.....	10	4	6	5	3	1	9	1
8.....	8	4	4	4	3	1	8	..
15.....	5	3	2	2	1	2	5	..
22.....	9	4	5	7	1	1	9	..
29.....	11	2	9	4	3	1	8	3
June 5.....	7	3	4	3	4	..	7	..
12.....	7	5	2	4	2	1	7	..
19.....	8	4	4	3	4	1	8	..
26.....	12	5	7	5	5	2	12	..
July 3.....	12	5	7	5	4	2	11	1
10.....	7	3	4	3	2	1	6	1
17.....	6	2	4	4	1	1	6	..
24.....	9	6	3	5	1	2	8	1
31.....	6	3	3	6	6	..
August 7.....	13	4	9	7	3	3	13	..
14.....	16	7	9	8	6	2	16	..
21.....	15	6	9	9	4	2	15	..
28.....	7	1	6	3	2	2	7	..

* The deaths occurring in children under 1 year of age was 52.2 per cent. of the whole number of deaths; 1 year and under 2, 30.3 per cent.; 2 and under 5, 14.2 per cent. The deaths occurring in those under 5 years of age was 96.9 per cent.; over 5, 3.1 per cent.

TABLE 2.—DEATHS FROM PERTUSSIS IN GREATER NEW YORK IN 1915, ACCORDING TO WEEKS, SEX AND AGE GROUPS—(Continued)

Week Ending	Total Deaths	Male	Female	Under 1 Year*	1 Year and Under 2	2 Years and Under 5	Total Deaths Under 5	Over 5 and Under 15
September 4.....	15	7	8	7	4	3	14	1
11.....	18	6	12	5	11	2	18	..
18.....	12	7	5	8	3	1	12	..
25.....	10	3	7	6	3	1	10	..
October 2.....	12	3	9	1	9	2	12	..
9.....	12	3	9	9	1	1	11	1
16.....	3	..	3	3	3	1
23.....	6	2	4	4	1	1	6	..
30.....	6	4	2	3	..	3	6	..
November 6.....	4	2	2	1	..	2	3	1
13.....	3	2	1	..	2	1	3	..
20.....	3	..	3	2	1	..	3	..
27.....	5	4	1	4	1	..	5	..
December 4.....	6	1	5	2	2	1	5	1
11.....	4	2	2	4	4	..
18.....	3	..	3	3	3	..
25.....	7	1	6	2	4	1	7	..
Total.....	385	157	228	201	117	55	373	12

* The deaths occurring in children under 1 year of age was 52.2 per cent. of the whole number of deaths; 1 year and under 2, 30.3 per cent.; 2 and under 5, 14.2 per cent. The deaths occurring in those under 5 years of age was 96.9 per cent.; over 5, 3.1 per cent.

During the same period we treated at the Whooping Cough Clinic 1,046 patients with true pertussis, of whom 465 (44.4 per cent.) were boys and 581 (55.6 per cent.) were girls. (See Table 3, in which 1,013 of these cases are recorded, there being no record of the age of the remaining thirty-three.)

Out of 8,520 cases which we tabulated according to sex, the proportion seems to be about the same, namely, 3,818 among boys (44.8 per cent.) and 4,702 among girls (55.2 per cent.).

The total number of deaths from pertussis in the former city of New York (Manhattan and Bronx) was, as stated above, 17,046. Of these deaths, 9,514 were among girls (55.8 per cent.) and 7,532 among boys (44.1 per cent.).

Figure 2 illustrates the relative number of these deaths for each year. It is interesting to note that the influence of sex is perceptible in all age periods. Thus, of the 8,668 deaths among patients under 1 year old (Table 1) there were 4,019 among boys (46.36 per cent.) and

TABLE 3.—INCIDENCE OF PERTUSSIS AND DEATHS ACCORDING TO AGE AND SEX, WITH RELATIVE PERCENTAGE

	Under One Year		One Year and Under Two		Two Years and Under Five		Five Years and Under Fifteen		Fifteen Years and Over		Total	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Cases at the Whooping Cough Clinic:												
Number.....	98	133	83	90	187	208	94	111	1	8	463	550
Percentage.....	42.4	57.6	47.9	52.1	47.3	52.7	45.8	54.2	11.1	88.9	45.7	54.3
Incidence as per Epidemiologic Surveys:												
Number.....	560	838	514	556	1,175	1,343	588	697	12	81	2,849	3,515
Percentage.....	40.05	59.04	48.03	51.09	46.66	53.33	45.75	54.24	12.90	87.09	44.76	55.23
Deaths in Manhattan and Bronx, 1866 to 1915:												
Number.....	4,019	4,649	2,030	2,629	1,303	1,910	183	288	7	28	7,532	9,514
Percentage.....	46.36	53.63	43.35	56.42	40.55	59.44	38.83	61.14	20.00	80.00	44.12	55.87

4,649 among girls (53.63 per cent.); and of the 4,659 deaths among patients under 2 years but over one year old, 2,030 were among boys (43.35 per cent.) and 2,629 among girls (56.42 per cent.). The deaths of those over 2 and under 5 years were 1,303 among boys (40.55 per cent.) and 1,910 among girls (59.44 per cent.). Those over 5 and under 15 years show a disproportion even more pronounced, namely, 471 deaths, of which 183 were among boys (38.83 per cent.) and 288 among girls (61.14 per cent.). It seems that with the accentuation of sex differences there is a higher proportion of deaths among girls as compared with the deaths among boys. Table 3 illustrates the interaction of the two factors of age and sex in both the incidence and number of deaths.

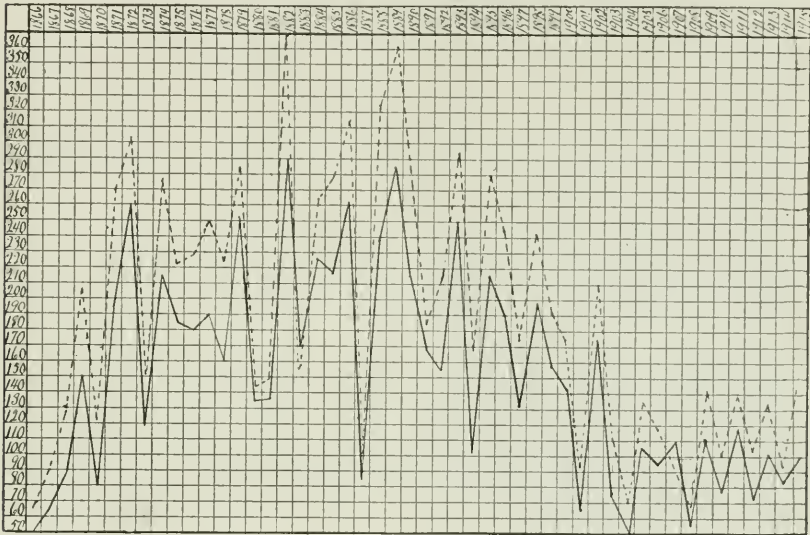


Fig. 2.—Deaths from pertussis in former city of New York for the last fifty years, from 1866 to 1915, according to sex. The solid line represents males, the dash lines females.

In adults there is even a much more marked disproportion between the sexes. Owing, however, to the small number of deaths, and especially to the greater exposure of the woman to infection from children, it would not be wise to draw conclusions specifically supporting the sex factor; but the figures of adult infection as well as mortality strongly suggest that the woman is more prone to contract pertussis and more often succumbs to it than the man.

During our epidemiological survey we tabulated 6,364 cases according to both age and sex. Their interrelation will be best seen in Table 3, where the number of cases at the Whooping Cough Clinic, as well as

the deaths for the last fifty years, are tabulated according to both sex and age.

It is quite apparent from these figures that in children and adults the female is more frequently infected with pertussis at all ages than is the male.

This predisposition to pertussis becomes more significant when we compare our tables to the general birth and death rate. In 1866, there were in Manhattan and Bronx, 10,107 children born, of whom 5,202 were boys and 4,905 girls; in 1912 there were 40,971 boys and 38,954 girls born. Hence, there is a slight excess in the birth of boys over that of girls. It is the same with the general mortality rate. Out of 31,937 deaths in 1880, a typical average year, there were 16,831 among males (rate 28.45) and 15,106 among females (rate 24.45). Of the deaths of those under 5 years, 7,912 were among boys (rate 111.7) and 6,738 among girls (rate 96.4). In 1912 there were 43,492 deaths, of which 12,819 were among those under 5 years of age, namely 7,050 boys (death rate 44.3) and 5,769 girls (death rate 36.9).

When we turn now to the mortality tables of other infectious diseases which mostly attack children, we find that in none of them is the sex factor of any significance.

In measles, for instance, there are generally more deaths among male than among female patients. In scarlet fever the mortality is variable; some years the deaths among female patients predominate, in others, those among male patients; as a whole there are more among male patients. In diphtheria and croup the same relations exist with a decided increase of deaths among boys under the age of 5. Deaths from bronchitis vary each year, but when several years are taken, there are decidedly more deaths among male patients; of those under 5 years of age, there is constantly a larger number of boys dying. In pneumonia this excess of deaths among males over those among females is even more pronounced.

Hence, we must consider pertussis as an exception to other infectious diseases by the constancy with which it attacks girls and the predisposition which girls seem to have to succumb to the infection more readily than boys.

THE FACTOR OF SEASONAL VARIATIONS IN PERTUSSIS

The relation of the seasons to the prevalence of pertussis is seemingly paradoxical. In its etiology, symptomatology and course, whooping cough is apparently an infection of the upper respiratory tract, and one would therefore expect it to be most prevalent and fatal during the fall and winter months. During our epidemiologic surveys it was found, however, that the actual state of affairs was just the opposite, most cases being reported during the spring and summer and most deaths occurring in the middle of the summer.

Thus, the 6,868 pertussis cases reported during the year 1915 were distributed as follows:

Month	Cases Reported	New Cases at Clinic	Deaths
January	341	140	14
February	381	65	16
March	452	91	16
April	462	112	42
May	754	114	43
June	599	231	34
July	843	253	40
August	906	348	51
September	640	295	55
October	543	181	39
November	458	173	15
December	389	157	20
Total	6,868	2,160	385

It will be seen from the above table that the number of new cases treated at the Whooping Cough Clinic was highest in August. It should be noted, however, that the relatively greater ease with which the clinic can be attended during the summer months might have slightly influenced the clinic figures; also that a certain percentage of these clinic cases were not true cases of pertussis.

The various surveys convinced me that most cases of pertussis seem to occur in the spring and summer. For obvious reasons no figures which would have any comparative value could be given here, as the investigations were not conducted during the whole of any year or month.

Figure 3 illustrates the number of cases reported to the department for the last ten years and also the number of deaths. It will be seen that the incidence seems to be largest in the spring; but it must be remembered that the morbidity records of pertussis are noncomparable and that many pertussis sufferers leave the city during the summer months for the seashore and hence are not reported. Complete returns would probably show the curve of morbidity reaching its acme in July, a few weeks before the height of the mortality in August.

The remarkable feature of the pertussis curve is that it coincides in most years more nearly with that of the diarrheal diseases rather than with that of the respiratory infections.

Figure 4 illustrates the seemingly opposite effect which the seasonal variation has on pertussis as contrasted to its effect on the mortality of scarlet fever, measles, diphtheria and croup and acute bronchitis. It will be seen that the lowest point reached by the curve of acute bronchitis coincides with the highest point of the curve of pertussis.

In the face of these facts, one must ask himself involuntarily whether the fatality of pertussis is not due to something besides the respiratory infection; whether a toxin similar to that produced by the

diarrheal diseases is not the direct cause of death. Another view would be that death during the summer is hastened by gastro-intestinal complications and that during the winter bronchopneumonia is the usual complication. The question is now being studied through careful analysis of the death certificates and other data. Judging from the death certificates one would say that diarrheas complicate only a relatively small number of pertussis cases.

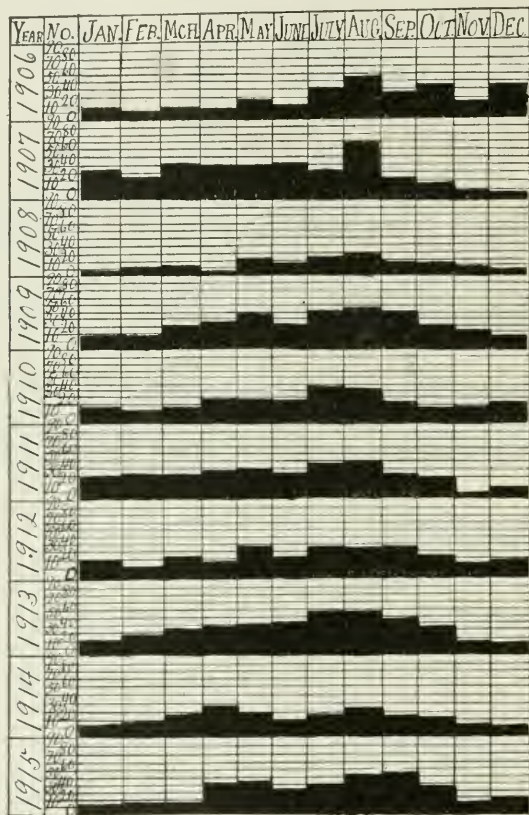


Fig. 3.—Deaths from pertussis by months for the last ten years, from 1906 to 1915.

THE FACTOR OF SURROUNDINGS IN PERTUSSIS

Most of the cases included in this study are of patients living in congested tenement districts, where the opportunities of infection are constant and many guardians are ignorant of the danger of the disease and its prevention.

Out of 162 investigated deaths, 160 occurred in tenement houses or in institutions to which these tenement patients were transferred after the onset of pneumonia. In all these cases there were more than three children in the family and in seventy-four the mother had to go out

working and leave the children in nurseries or in the care of neighbors. The average number of rooms occupied by the family is a little less than two and a fourth, a large number occupying only one or two rooms.

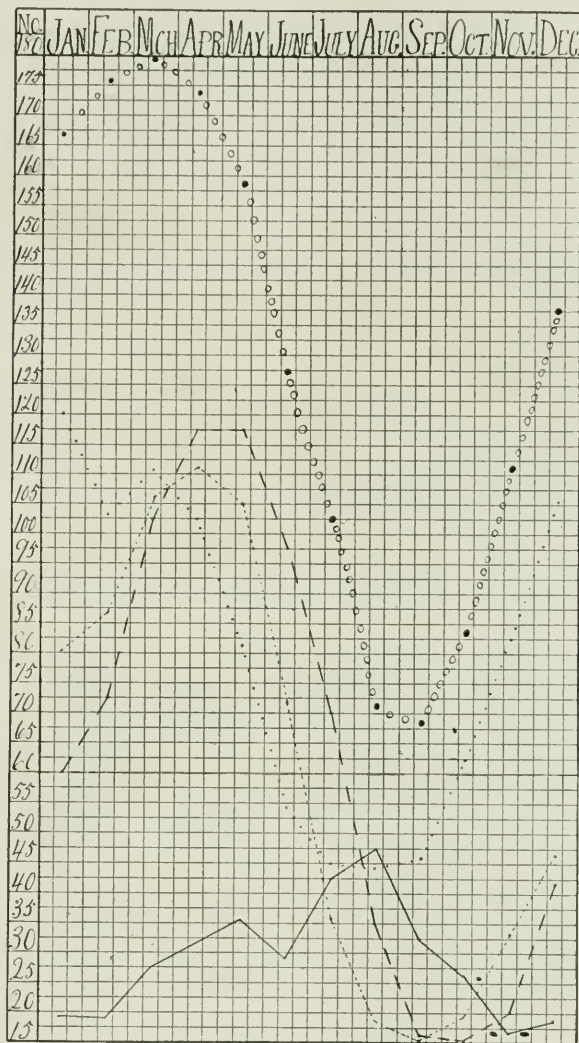


Fig. 4.—Average yearly deaths from certain infectious diseases by months, for the decade 1905 to 1914. Solid line indicates pertussis; line of long dashes, measles; short dashes, scarlet fever; dotted line, acute bronchitis, and the line of rings, diphtheria and croup.

Although I have no extensive data on the subject, it is my impression as I examine case after case at the Whooping Cough Clinic that the children who whoop longest and most severely lack sufficient fresh air and suffered from malnutrition before they contracted pertussis.

Of the 182 cases in private practice, there was not a single death, although many of them were very severe and several patients contracted pneumonia. Fresh air seemed to have a decidedly favorable effect on the course of the disease.

Apparently, it is not the fresh air *per se* which is so effective, but the change of air. Change of surroundings in themselves seem to have a beneficial effect, even if the amount or quality of the air is not appreciably different from the former surroundings. To this fact may perhaps be ascribed the prevalent "superstition" that the neighborhood of gashouses is beneficial to pertussis.

We often see patients at the clinic who reside in Manhattan tenements and who have relatives in East New York living in equally congested districts or vice versa, and a visit from one congested district to another seems to be so beneficial that it is often extended until the patient stops whooping.

Two patients with pertussis, said to have contracted the disease on a transatlantic liner (probably not on the liner, but on land before sailing), stopped whooping when they set foot in New York. Another, who apparently developed pertussis on a steamboat, began to whoop two days after landing and was severely ill for four weeks without improving in spite of a well-ventilated, sunny room. He was finally taken to Lakewood, where the paroxysmal cough subsided a day after arrival.

It seems, therefore, that the ideal place for the treatment of pertussis patients would be a ferry-boat with open wards on the decks and which could make occasional trips to different points of the harbor. Such a ferry could also be moored to certain piers and clinics held for pertussis sufferers in the neighborhood. Such a boat camp, to my estimation, would solve the problem of efficiency caring for the numerous patients having whooping cough in the city, especially during the summer months. A hospital for pertussis patients only and specially designed for the purpose would be the next choice.

In sparsely populated districts, like the boroughs of Richmond and Queens, there is apparently very little pertussis.

MORTALITY IN PERTUSSIS

For reasons sufficiently discussed before, it is extremely difficult to arrive at the actual case incidence mortality. The failure to report all cases of pertussis, and especially the mild atypical cases, precludes the possibility of arriving at complete statistics on the subject.

During the preliminary survey we found, for instance, seven deaths out of 161 actual pertussis cases, which gives a case mortality of 4.3 per cent. Of all cases investigated during the last three years, we find that there is a record of 210 deaths out of 8,310 cases; but in view of

the irregularity as to the seasons and the impossibility of revisiting these patients, hardly any account of these figures can be taken.

A more accurate, though incomplete, estimation may be made by comparing the number of deaths from whooping cough in the city of New York in 1915 with the number of cases reported. These figures are 385 and 6,868, respectively, and show a case mortality of 5.60 per cent. The actual case mortality, when one takes into consideration the unreported and atypical cases and those among adults, is probably from $\frac{1}{2}$ to 1 per cent.

As to the relation of pertussis to the general death rate, it may be studied from Table 4, which gives the death rate of pertussis per 100,000 population in the former city of New York (Manhattan and Bronx) also the annual deaths and death rate per 1,000 population since 1868.

TABLE 4.—PERTUSSIS DEATH RATE AS COMPARED TO GENERAL DEATH RATE, FORMER CITY OF NEW YORK

Year	Population	Total Deaths	Death Rate per 1,000 Population	Deaths from Whooping Cough	Rate per 100,000 Population
1868	851,137	24,889	29.24	217	25.50
1869	896,034	25,167	28.08	358	39.96
1870	943,300	27,175	28.80	201	21.31
1871	955,921	26,976	28.22	465	46.65
1872	968,710	32,647	33.70	565	58.32
1873	981,671	29,084	29.63	268	27.31
1874	1,030,607	28,727	27.89	489	47.47
1875	1,044,396	30,709	29.40	407	38.97
1876	1,075,532	29,152	27.11	406	37.76
1877	1,107,597	26,203	23.66	440	39.76
1878	1,140,617	27,008	23.67	382	33.50
1879	1,174,621	28,342	24.13	537	45.72
1880	1,209,196	31,937	26.42	277	22.92
1881	1,244,511	38,624	30.75	286	22.98
1882	1,280,857	37,924	29.61	658	51.38
1883	1,318,264	34,011	25.81	327	24.81
1884	1,356,764	35,034	25.83	490	36.12
1885	1,396,388	35,682	25.56	495	35.45
1886	1,437,170	37,351	26.00	575	40.02
1887	1,479,143	38,933	26.33	188	12.71
1888	1,522,341	40,175	26.39	573	37.64
1889	1,566,801	39,679	25.36	647	41.30
1890	1,612,559	40,103	24.87	487	30.20
1891	1,659,654	43,659	26.31	352	21.21

TABLE 4.—PERTUSSIS DEATH RATE AS COMPARED TO GENERAL DEATH RATE, FORMER CITY OF NEW YORK—(Continued)

Year	Population	Total Deaths	Death Rate per 1,000 Population	Deaths from Whooping Cough	Rate per 100,000 Population
1892	1,708,124	44,329	25.95	371	21.72
1893	1,758,010	44,486	25.30	542	30.83
1894	1,809,353	41,175	22.76	272	15.03
1895	1,873,201	43,420	23.18	496	26.48
1896	1,906,139	41,622	21.84	435	22.28
1897	1,940,553	38,877	20.03	308	15.87
1898	1,976,572	40,438	20.46	442	22.36
1899	2,014,330	39,911	19.81	350	17.38
1900	2,055,714	43,227	21.03	318	15.47
1901	2,118,209	43,304	20.45	159	7.50
1902	2,182,836	41,704	19.11	385	17.64
1903	2,249,680	41,776	18.57	187	8.31
1904	2,318,831	48,743	21.02	120	5.17
1905	2,399,041	45,199	18.91	239	10.00
1906	2,460,456	46,108	18.74	202	8.21
1907	2,534,454	47,698	18.82	201	7.93
1908	2,612,322	44,061	16.82	123	4.71
1909	2,694,373	44,387	16.47	254	9.43
1910*	2,777,542	45,628	16.44	177	6.76
1911*	2,849,635	45,324	15.91	256	8.98
1912*	2,921,728	43,492	14.89	176	6.02
1913*	2,993,821	43,189	14.43	235	7.85
1914*	3,065,914	43,253	14.21	175	5.71
1915*	3,138,007	43,794	13.96	264	8.41

* Corrected population figures as per U. S. census estimates.

It will be seen that the death rate has steadily decreased from 25.5 per 100,000 population to about 7. It is interesting to note that it went up as high as 58.82 and that it was frequently four to five times its present rate. The lowest rate was 4.71 in 1908. Besides the general tendency toward a lower death rate, no rhythm of any kind can be discerned; the number of deaths for each seems to be independent of any meteorologic or other uncontrollable agencies. The steady lowering of the death rate is probably due to the general increase in knowledge and observation of public and personal hygiene.

One cannot refrain from comparing this lowering of the pertussis death rate with that of diphtheria. Although no specific therapy had been used in whooping cough until recently it compares favorably with the diphtheria curve influenced by antitoxin.

SOURCES OF INFECTION—PERTUSSIS CARRIERS

The sources of infection in whooping cough are in the majority of cases easily ascertained. In a certain percentage of cases, however, it is obscure and can only be determined after a painstaking investigation. Only in a very limited number of apparently sporadic cases does the source of infection remain undiscovered. Those baffling cases escape detection only through lack of intelligent observation on the part of the guardian.

The infection in pertussis is undoubtedly transmitted through direct contact. While infection through the common use of pencils and other personal articles may and probably does occur, there is always enough personal contact between the diseased and the healthy child not to exclude direct transmission as well as indirect infection.

At the suggestion of Dr. Williams, special attention was paid, in our epidemiologic investigation, to the presence of domestic animals in the houses of those suffering from pertussis. Out of 1,120 homes visited, we found only twenty-six which harbored such pets, namely, fifteen dogs, eight cats, one rabbit, one monkey, one turtle. With one exception, none of these animals had any cough, and in view of the fact that we have been unable so far to transmit pertussis to puppies and rabbits, it is hardly probable that these animals could become factors in the transmission of the disease. One dog (a Newfoundland) was found in a Staten Island home to have a hoarse cough; but the animal had been sick with rheumatism for nearly a year. I asked permission to take a culture from the dog's throat, having in mind the *Bacillus bronchisepticus*, which morphologically resembles the Bordet-Gengou bacillus; but owner refused, stating he did not believe in "vivisection." Two weeks later he telephoned me that he was willing to let me take the culture, but I was unable to go out that day, and the dog died the following morning.

At the Whooping Cough Clinic a careful record was kept of the alleged sources of infection. The analysis of 2,310 actual cases of pertussis gives the following results:

Probable Source of Infection	No. Cases
Neighbor	1,311
Relative or friend.....	204
Playmate	203
School	146
Nursery	76
Moving pictures	62
Recreation pier	18
Roof garden	9
Ferry	8
Street (?)	6
Subway, elevated and street cars.....	4
Unknown	263
Total	2,310

Thus, nearly 60 per cent. of all sources of infection were ascribed to neighbors' children who were suffering from the disease. The next two largest figures, but only about 10 per cent. each of the total, are blamed on relatives and playmates. The school was accused in only about 7 per cent. of the cases. An interesting though small factor seems to be the recreation piers, roof gardens and ferries, where people usually go to escape the infection of the crowded tenement.

The moving-picture shows as sources of infection became the subject of a special investigation. During the spring, summer and autumn of last year I visited off and on quite a number of cinematograph shows and found them to be ideal dissemination grounds for pertussis and possibly other diseases.

The better class of cinemas, in the central part of the city, do not admit children in arms; but the 5-cent shows, which are fortunately decreasing in number, and also some 10-cent places in the congested districts on the East Side, Brooklyn, Harlem and the Bronx, cater to the family trade, and many of them have as a special convenience for their patrons a "baby carriage garage." The baby is either left in the carriage or taken inside; the other children are invariably taken in unless they are too sick to leave their beds. It is rare in visiting some of these crowded shows not to hear continued coughing, from the short, plain, bronchial cough to the long-drawn-out, severe whoop. Table 5 will give one an idea of the actual state of affairs.

TABLE 5.—CINEMAS AS SOURCES OF INFECTION

Month, 1915	Number of Cinemas Visited	Number of Children Whooping	Number Having Paroxys- mal Cough	Number Having Plain Cough	Number of Adults Coughing	Number Cinemas Using Atomizers
March.....	10	1	5	6	2	8
June.....	14*	2	2	8	0	4
July.....	12†	2	0	5	1	1
September.....	20‡	5	11	2	8	5
October.....	15	2	2	4	22	10
November.....	14	0	1	2	30	6
December.....	9	0	0	8	52	8
Total.....	94	12	21	35	63	42

* Four open air.

† Ten open air.

‡ Three open air.

Another objectionable feature of these shows is the use of the so-called perfume atomizer tabulated in the last column of Table 5. It is operated by one of the attendants, whose duty it is to spray the premises at regular intervals during the performance. He walks up

and down the aisles using as much strength as possible, so that the perfume may reach at least to the center of the row of seats. It does not require much imagination to see how the sputum droplets from a child who coughs may be carried by these vigorous air currents to an unlimited number of spectators. Besides this, a false feeling of security is promoted among the public by disguising the foul air and thereby discouraging the proper ventilation of the premises.

Crowded cars as possible sources of infection were brought to my attention by the following case: A woman with two children boarded a Second Avenue elevated train at 105th St., and sat opposite another woman with three children who looked perfectly normal. A few stations farther downtown one of the children began to whoop and was taken care of by the mother, who put a handkerchief in front of his mouth and bent his head to the floor. Presently the second and then the third child began to cough and vomit, and she naturally could not attend to all of them at once. The car being crowded, it was impossible for the woman with the two healthy children to alight before 59th St. About two weeks later she applied to the Whooping Cough Clinic for treatment and gave the above history of infection.

Of the 263 cases of pertussis whose source of infection was not known by the parent, I visited about ninety. Nearly all of these, after careful cross examination of the parents, could be ascribed either to a neighbor's child or to some friend whose visit had been forgotten.

Carriers.—Eight patients undoubtedly were infected by the kiss of adults whose children had the whooping cough but had never been in contact with these patients, as they lived in different parts of the city. All these adults had a "little cough," which lasted for five or six weeks, and had all the earmarks of typical carriers.

An interesting pertussis carrier was Peter G., who boarded with his sister in Harlem. Two nieces and one nephew contracted whooping cough from their neighbors and Peter began to cough a few weeks later. About the beginning of March he visited a sister living in Brooklyn with the view of reconciling her to the Harlem sister, from whom she had been estranged. About eight days later one of the children began to cough. March 10 the Brooklyn sister visited her Harlem relative alone, made up with her and told her of her children, who were whooping. Both sisters finally met at the Whooping Cough Clinic a week later. In the meantime, Peter left his Harlem sister and went to live with his brother, who had just come from some Pennsylvania town; he was still coughing. A week later one of this brother's children began to cough and a few days later started to whoop and vomit. The other child had had whooping cough before. The father now accused Peter of having given the disease to the child and they quarreled, Peter going to live with a cousin (a bachelor) in East Twelfth

St. On April 14 one of the neighbor's children began to whoop, and as there was no pertussis cases in that house, we finally traced the source of infection to Peter, who was still coughing, and asked him for his sputum. This he delayed until April 20, when he sailed for Italy, having enlisted in the army. He sent a sputum jar to the laboratory on that day, but it was found later that it was his cousin's sputum, who was perfectly normal. The child who had contracted pertussis from Peter told me that Peter often kissed her and gave her pennies because she looked so much like his niece in Harlem. We have surnamed this carrier "Pertussis Pete," and trust that he will be spared by the enemy and return to New York so that we may complete our records.

Natural Immunity.—During the preliminary survey I was impressed with the apparent immunity that children of all ages seemed to exhibit. Thus, out of ninety-two families visited in which whooping cough had occurred I found that in twenty-seven of them (29.3 per cent.) there were one or more children of susceptible age who had failed to contract the disease. Subsequently, however, it was found that in the great majority of these cases, after careful cross examination, a history of a mild cough without the characteristic paroxysms could be obtained; many of them having had vomiting spells which had been forgotten by the parents. A certain number of these apparently immune children could also be ruled out because of their slight contact with the infected ones or entire absence from home during the attack. Nevertheless, there seems to be a certain indefinite percentage who do not contract the disease or who do not show any symptoms of it.

Of a total of 840 families (3,100 children) visited and questioned with the subject of natural immunity in view, I found 270 (914 children) in which one or more children had had apparently atypical attacks of the disease; 61 of these children were apparently immune; 42 had had pertussis before and the rest (811) were probably abortive cases. Among these 811 there were 69 who had had whooping cough before.

As a contrast I found only 18 children among 9,400 with an apparent second attack of pertussis (with typical whoop).

INFLUENCE OF SPECIFIC VACCINES ON THE EPIDEMIOLOGY OF PERTUSSIS

The pertussis stock vaccines as prepared in the Bureau of Laboratories have not been long enough used or in sufficiently general use to lend themselves to deductions regarding their influence on the morbidity or mortality. One impression, however, has been that, judging from the results obtained at the Whooping Cough Clinic and by about forty private physicians and health officers in this and other cities, they have undoubtedly reduced the number of deaths and prevented the spread of the disease.

The good results reported last year by myself² have continued, and when the proper vaccines are used, there has been a further shortening of the paroxysmal stage and a reduction in the severity and number of the paroxysms. Dr. Hoag, in charge of the Children's Clinic at St. Mary's Hospital and Dispensary, in a paper read before the Bellevue Hospital Alumnae Association, has reported a large number of patients who have been cured and many in whom the disease has been prevented by our vaccines; his results, owing perhaps to a better class of patients, have been even more brilliant than those at the Whooping Cough Clinic.

Out of 2,103 patients with pertussis, 75 per cent. of whom were treated with vaccines and were followed up by the Clinic nurse, we had fourteen deaths. Ten of these were treated by drugs and one injection of the vaccine. The other four were treated by vaccines exclusively, two of them being commercial mixed vaccines and two others our laboratory stock vaccines. These two died in convulsions. Four more deaths occurred at the Reception Hospital, but the patients had been brought to us moribund and we can draw no conclusions whatever from their deaths except that neglected nursing at home (mothers had to go out working) probably contributed to the fatal outcome.

We have not had a single death in patients brought to us before the third week of the paroxysmal stage and who presented themselves for vaccine treatment at regular intervals. This fact alone seems to warrant the establishment of more Whooping Cough Clinics.

As to prophylaxis, while we still lack the absolute proof that pertussis vaccine is a positive prophylactic agent, data are accumulating which strengthen our belief that it acts as such in all patients who are inoculated before any symptoms develop and that in many cases it aborts the disease. Whether such prophylactic cases would have remained free from pertussis even without the administration of the vaccine is a question which cannot be solved in private or dispensary practice.

SUMMARY

Epidemiologic studies in Whooping Cough conducted by the Research Laboratory shows that pertussis is a very prevalent disease in New York City, and that probably only a tenth of all cases are reported to the Department of Health.

About 80 per cent. of all cases and 97 per cent. of all deaths are in children under 5 years of age. Fifty per cent. of the cases are in those under 2 years of age, and over 50 per cent. of all deaths are in children under 1 year of age.

2. Luttinger: Whooping Cough, Its Treatment and Prophylaxis, Based on the Bordet-Gengou Etiology, *New York Med. Jour.*, May 22, 1915.

The incidence of pertussis among girls, as well as the number of deaths, is constantly higher than among boys, the proportion of both morbidity and mortality being about 44 per cent. for boys and 56 per cent. for girls.

In contradistinction to other respiratory diseases, whooping cough seems to be most prevalent in the spring and summer months and the mortality curve reaches its highest point in August, showing a similarity to the diarrheal diseases, although most deaths are due to pertussis pneumonia.

Poor surroundings, congestion, lack of fresh air and proper care due to the guardian's precarious economic status seem to have a determining effect on both the morbidity and mortality of pertussis.

The actual case mortality in whooping cough is difficult to estimate, owing to incomplete returns; it is probably about 1 per cent. The death rate per 100,000 population is about 7. It has been steadily decreasing for the last fifty years having been as high as 58.82 in 1872 and as low as 4.71 in 1908.

Whooping cough is transmitted by direct contact and in nearly 60 per cent. of cases the source of infection is given as coming from a neighbor. Relatives and friends, schools, nurseries, recreation piers and ferries are other sources of infection. Moving picture shows and public conveyances seem to be important factors in the dissemination of the disease.

Adult pertussis carriers probably have been disseminating the disease and have remained unrecognized owing to the atypical form in which it manifests itself.

Pertussis vaccines, as prepared by the Bureau of Laboratories, when given early, have continued to give good curative and prophylactic results at the Whooping Cough Clinic and in the hands of a large number of private practitioners and health officers. The very small number of deaths under vaccine treatment and the vast crowds who apply for treatment at the clinic indicate a favorable and possibly tangible influence of the specific treatment on the further epidemiology of the disease.

CONCLUSIONS

Measures should be adopted to reduce the morbidity and mortality of pertussis, special attention being paid to children under 1 year of age in the spring and summer months. These measures should include the following:

1. Education of the private physicians as to the prevalence and fatality of the disease and the securing of his cooperation in reporting all pertussis cases and in using the specific vaccines wherever practicable as a prophylactic and in early cases.

2. The education of the laity through physicians, nurses, leaflets, etc.
3. Regulation of moving-picture shows and other public meeting places, which should as far as possible exclude children with paroxysmal coughs.
4. Quarantine of pertussis cases during the first two weeks of the disease.
5. The establishment of more whooping cough clinics, at least one in each borough.
6. The organization of a boat camp for the rational treatment of pertussis, especially during the summer time, should be carefully considered.
7. The use of a suitably constructed pertussis hospital, in which the care of patients with severe attacks of whooping cough could be more efficiently undertaken and which would afford an opportunity for further scientific research on laboratory as well as clinical lines.

My thanks are due to Mr. J. H. Gibbons of the Bureau of Records for statistical transcriptions from the Department of Health records and for other courtesies. To the Misses Loretta Smith and Florence Walters, the very efficient nurses of the Whooping Cough Clinic, who did most of the follow-up work, I am greatly indebted for the successful completion of this study.

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AN ANAPHYLACTIC SKIN REACTION TO DIPHTHERIA BACILLI *

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PHILADELPHIA

The intracutaneous toxin test of Schick for antitoxic immunity in diphtheria may be stated to have definitely established itself as a safe, easily applied and reliable practical test for detecting those persons who have sufficient natural diphtheria antitoxin in their body fluids to protect them against this infection and also as a measure of antitoxin production after active immunization with toxin-antitoxin mixtures, the latter being the original purpose of Schick in working out the technic of this test to replace the more expensive, time consuming and laborious procedure of determining the antitoxin content of a serum by means of injecting mixtures of the serum and a toxin into guinea-pigs.

The positive toxin reaction is a localized inflammation excited by the unneutralized toxin in the skin, and in the majority of instances the area of erythema and edema is sufficiently well marked at the end of forty-eight hours to permit the proper interpretation of the test.

The practical value of the test, however, is impaired by the occurrences of false reactions among immune and nonimmune persons alike, first described by Park, Zingher and Serota,¹ and regarded by them as being local anaphylactic reactions to the protein of the broth and autolyzed diphtheria bacilli contained in the toxin broth. To this reaction they have applied the term "pseudo Schick reaction."

As the skin is a very delicate reacting medium, inflammatory reactions may be caused by a variety of factors. In a study of pseudoreactions with particular reference to those caused by trauma and the protein constituents of the broth alone² we found that trauma due to the injection of a fluid containing a preservative into the epidermis of persons whose skins are for some reason unduly sensitive plays an

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* From the McManes Laboratory of Experimental Pathology of the University of Pennsylvania and the Laboratory of the Philadelphia Hospital for Contagious Diseases.

1. Park, W. H., Zingher, A., and Serota, H. M.: The Schick Reaction and Its Practical Application, *Arch. Pediat.*, 1914, xxxi, 481.

2. Kolmer, J. A., and Moshage, E. L.: A Note on the Occurrence of Pseudo-reaction on the Skin with Special Reference to the Schick Toxin Test, *Jour. Am. Med. Assn.*, 1915, lxxv, 144.



Positive diphtherin reaction in M. A., aged 6 years; pustular reaction seventy-two hours after the intracutaneous injection of 0.1 c.c. of diphtherin. The patient reacted negatively to the Schick toxin test.



important part in the production of slight inflammatory reactions. As pointed out by us, this condition of peculiar skin hypersensitiveness was found especially among persons suffering or convalescent from scarlet fever and measles.³ Likewise the amount of fluid injected was found to influence the percentage of pseudoreactions, fewer being observed when the proper dose of toxin was contained in 0.1 c.c. than in 0.2 c.c. Furthermore, the sharp, stinging pain experienced during the injection, when it is properly given intracutaneously, is much less with 0.05 or 0.1 c.c. than with 0.2 c.c. For these reasons we dilute our toxin for the Schick test in such manner that the proper dose is contained in 0.1 c.c. of fluid.

The amount of protein substances injected in the broth used in the preparation of toxin was found to have less influence on the question of false reactions than the total amount of fluid injected. Reaction to the protein substances and various extractives from veal and beef may be due to their purely irritative character or to a general and nonspecific anaphylactic-like reaction explainable on the basis of the hypothesis advanced by Jobling and his colleagues that these substances may bring about a local release of proteolytic ferments by removing through absorption the unsaturated fatty acids or antitrypsin, followed by the digestion of the patient's own serum protein and the formation of toxic substances capable of producing an inflammatory reaction.

The reactions due to trauma and the substances contained in broth are rather poorly colored and defined, irregular in outline, measuring roughly about 0.5 by 0.5 cm., but being sometimes much larger, and accompanied by slight edema. The great majority subside within forty-eight hours, and for this reason the Schick test should not be read within the first twenty-four hours after the injection of the toxin.

It is apparent, therefore, that one variety of the pseudoreaction due to trauma, skin hypersensitiveness, and the various constituents of broth may be limited to some extent by attention to such details as the employment of a fine needle; a highly potent stock toxin that requires high dilution in order to obtain the proper dose for the Schick test, thereby reducing the amount of broth constituents injected; the injection of a minimum amount of fluid and waiting whenever possible for forty-eight hours before reading the results.

Of greater interest are the allergic or anaphylactic reactions to the protein of the diphtheria bacillus. The disease diphtheria is so widespread and so large a proportion of persons carry or have carried diphtheria bacilli in the nose, throat or ears that it may be well expected that a large number of persons will exhibit a condition of hypersensitiveness to the diphtheria protein.

3. Kolmer, J. A., and Moshage, E. L.: The Schick Toxin Reaction for Immunity in Diphtheria, *AM. JOUR. DIS. CHILD.*, 1915, ix, 189.

We were influenced toward making the studies recorded in this paper not only on account of the general importance of allergy in diphtheria, but also on the basis of the claims set forth by Gay and his associates that allergic skin reactions may be regarded as an index to immunity. If this is true it may be possible to shed more light on the immunity in diphtheria by means of an anaphylactic or allergic skin reaction, and show that resistance to diphtheria is not entirely or purely antitoxic in character and explain in part why some persons who give a positive Schick reaction do not contract diphtheria even though exposed to this infection.

MATERIALS AND METHODS OF STUDY

In this investigation we have conducted the anaphylactic skin reactions with an emulsion of washed and heat-killed diphtheria bacilli, for which we propose the name "diphtherin"; at the same time the regular Schick test was conducted in each person.

Preparation of Diphtherin.—The diphtherin used in this study was prepared of forty-five different strains of diphtheria bacilli freshly isolated (from three to thirty days previously) from the throats, noses and ears of persons suffering with diphtheria and convalescent from this infection. The types of bacilli contained thirty-three cultures of granular types, eight cultures of long, solid types, and four cultures of short, solid types.

Each culture was grown in glucose broth for four days and all mixed in a single flask and shaken mechanically with glass beads to break up clumps. To each 100 c.c. of the emulsion was added 5 c.c. of sterile horse serum antitoxin (2,500 units) and the whole shaken at room temperature for four hours. After this time the emulsion was placed in sterile centrifuge tubes and the bacilli separated and washed twice with large volumes of sterile normal salt solution. After the final washing the bacilli were resuspended in sufficient sterile salt solution to make, after thorough shaking, about two billion bacilli per cubic centimeter. This emulsion was heated at 60 C. for an hour, cultured for sterility and preserved with 0.2 per cent. tricresol. Subcutaneous injection of 1 and 2 c.c. into 250-gm. guinea-pigs showed absolutely no evidences of local reaction or general toxemia. In conducting the test, 0.1 c.c. of the emulsion was injected intracutaneously in the arm.

Preparation of Toxin.—The toxin for the Schick test was prepared by diluting a toxin (L + dose 0.625 c.c.) 1 to 100 with normal salt solution and determining the minimal lethal dose in a series of guinea-pigs weighing from 250 to 300 gm.; one-fortieth this amount was used

as the dose in conducting the toxin test. Sufficient normal salt solution containing 0.25 per cent. tricoresol was added to dilute the dose of toxin to 0.1 c.c., which amount was injected intracutaneously.

THE DIPHTHERIN REACTION

All reactions were recorded after an interval of forty-eight hours following injection, in order to permit the subsidence of the purely irritative reaction due to trauma, as previously pointed out.

Two types of reactions were observed. The first resembled the luetin reaction in all its essential details, being a circumscribed area of erythema accompanied by marked edema. The majority of these reactions were popular in character, while some were distinctly pustular (see accompanying figure). The height of reaction was usually reached in from forty-eight to seventy-two hours, when subsidence began, to be followed by a small reddish nodule which persisted for several days.

The second type of reaction corresponded quite closely with that described by Park and Zingher, being of early development (maximum in twenty-four hours) and marked by a wide and poorly circumscribed pinkish zone or cutaneous blush, with a smaller and redder area about the site of injection. This type of reaction when once seen is comparatively easy to distinguish from the true Schick toxin test, while it is frequently impossible to differentiate between the former type of diphtherin and the toxin reactions.

The Schick reactions were characterized by areas of erythema, with a brownish tinge measuring from 0.5 to 2 cm. in diameter and accompanied by slight edematous infiltration of the underlying tissues. After from forty-eight to seventy-two hours these reactions began to fade, leaving a pigmented area with slight superficial desquamation.

In a number of instances the toxin reaction showed a wide area of cutaneous blush, with a smaller area about the site of inoculation of deeper erythema with a brownish tinge and marked edema. All persons reacting in this manner gave positive reactions to the diphtherin alone and indicated thereby that the reactions to the toxin were a combined toxin and anaphylactic response.

THE DIPHTHERIN REACTION IN PERSONS OF VARIOUS AGES

The diphtherin and toxin tests were applied to 188 persons of various ages, most of whom were apparently healthy and well and had never had diphtheria or received an injection of diphtheria anti-toxin. A few were convalescent from scarlet fever or suffering with various chronic ailments and were tested while undergoing observation and treatment in the wards of various hospitals in Philadelphia. The results are summarized in Table I.

TABLE 1.—THE DIPHtherin AND TOXIN SKIN REACTIONS IN PERSONS OF VARIOUS AGES

Age, Years	Total Tested	Diphtherin Reactions			Toxin Reactions		
		Positive	Negative	Per Cent. Positive	Positive	Negative	Per Cent. Negative
Under 1.....	17	15	2	88	3	14	82
1 to 4.....	41	29	12	70	23	18	44
4 to 8.....	23	17	6	73	12	11	47
8 to 12.....	10	7	3	70	3	7	70
12 to 20.....	10	3	7	30	2	8	80
Over 20.....	87	40	47	45	33	54	62
Total.....	188	111	77	..	76	112	

As a negative toxin and a positive diphtherin reaction are regarded as indicating the presence of an antitoxic and anaphylactic antibody, respectively, the percentage of negative toxin and positive diphtherin reactions are given.

As shown in Table 1, a surprisingly large percentage of persons reacted in a positive manner to the diphtherin test. The majority of these reactions were of papular variety.

The larger percentage of positive anaphylactic reactions observed with diphtherin than with the protein contained in the dose of toxin used in the Schick test is to be expected on account of the larger amount of diphtheria protein injected. Thus the protein in the toxin test may produce about 30 to 35 per cent. anaphylactic reactions, while the percentage of reactions to diphtherin is much higher.

Children under 1 year of age showed the highest percentage of positive diphtherin reactions, 88 per cent.; among children from 1 to 12 years of age positive reactions were observed in about 70 per cent. Adults were found to react less frequently, about 75 per cent. of reactions being positive. Very young and poorly nourished infants usually fail to react in a definite manner, although small and poorly defined areas of erythema and edema may be detected. The results of the toxin tests were closely similar to those found in our previous work.

Both antibodies, namely, antitoxin and anaphylactic antibodies, were found in highest percentage among children under 1 year of age; after that age the percentage of persons showing anaphylactic antibodies gradually decreased, the lowest percentage of positive diphtherin reactions being found among adolescents and adults. Antitoxic immunity (negative Schick tests). on the other hand, has been generally found in from 65 to 90 per cent. of persons over 15 years of age.

The largest percentage of persons were found to react positively to the diphtherin and negatively to the toxin tests, indicating the presence of anaphylactic and antitoxic antibodies; some reacted negatively to the diphtherin and positively to the toxin tests, indicating the absence of both antibodies; others were positive (anaphylactic antibodies present and antitoxin absent) or negative (anaphylactic antibodies absent and antitoxin present) to both. The results among 188 persons were as follows:

1. Those reacting positively in the diphtherin and negatively in the toxin tests were 53.3 per cent.
2. Those reacting negatively in the diphtherin and positively in the toxin tests were 10 per cent.
3. Those reacting positively in both tests were 12.5 per cent.
4. Those reacting negatively in both tests were 24.1 per cent.

In other words, the serums of about 50 per cent. of persons contain both natural antitoxic and anaphylactic antibodies; only 10 per cent. of persons were found to contain neither of these antibodies. About 24 per cent. of persons showed the presence of antitoxic and absence of anaphylactic antibodies and only 12.5 per cent. the presence of anaphylactic and the absence of antitoxic antibodies.

If a positive diphtherin reaction may be interpreted as indicating a condition of lytic immunity, as a negative toxin test of Schick is regarded as indicating an antitoxic immunity, it is to be noted that the diphtherin test agreed with the toxin test in 63 per cent. of cases. In 37 per cent. of persons the results differ, and largely (24 per cent.) to the effect that persons may possess natural antitoxin, and thereby yield negative toxin reactions, but with no anaphylactic antibodies, and thereby yield negative diphtherin reactions.

If immunization with diphtheria antitoxin were guided by the results of these tests, the diphtherin test would reduce the number of persons requiring passive immunization by about 12 per cent., as this percentage was found to yield positive allergic reactions and the blood serums no antitoxin.

THE DIPHTHERIN REACTION AMONG PERSONS WHO HAD RECEIVED DIPHTHERIA ANTITOXIN

We have applied the diphtherin and toxin tests to sixty-one children receiving curative or prophylactic doses of diphtheria antitoxin with the result shown in Tables 2 and 3.

No opportunities were afforded for applying the tests to persons having diphtheria, or to those recovering from the disease, who had not received antitoxin.

TABLE 2.—THE DIPHTHERIN AND TOXIN SKIN REACTIONS AMONG PERSONS SUFFERING WITH DIPHTHERIA AND RECEIVING ANTITOXIN

Number	Age, Years	Diagnosis	Antitoxin Units	Days after Anti-toxin	Reactions	
					Diphtherin, Cm.	Toxin, Cm.
1	11	Tonsillar diphtheria.....	12,000	8	1.5 × 1.5	1 × 1
2	11	Tonsillar diphtheria.....	20,000	11	1 × 1	—
3	3	Tonsillar diphtheria.....	15,000	12	—	—
4	4	Tonsillar diphtheria.....	50,000	14	—	—
5	3	Tonsillar diphtheria.....	12,000	15	0.6 × 0.0	—
6	3	Tonsillar diphtheria.....	12,000	15	0.6 × 0.6	—
7	8	Tonsillar diphtheria.....	5,000	15	2 × 2.5	1 × 1.5
8	7	Laryngeal diphtheria.....	20,000	17	—	—
9	3	Tonsillar diphtheria.....	15,000	17	1 × 1	—
10	5	Laryngeal diphtheria.....	25,000	18	1 × 1	—
11	3	Laryngeal diphtheria.....	15,000	18	0.6 × 0.6	—
12	8	Tonsillar diphtheria.....	30,000	19	1 × 1.05	—
13	5	Tonsillar diphtheria.....	20,000	18	0.6 × 0.6	—
14	8	Positive culture case.....	8,000	20	1.5 × 1.5	1.5 × 1.5
15	4	Tonsillar diphtheria.....	30,000	22	1 × 0.7	—
16	3	Tonsillar diphtheria.....	20,000	22	1 × 1	—
17	11	Laryngeal diphtheria.....	17,000	26	1 × 1	—
18	8	Tonsillar diphtheria.....	30,000	28	1 × 0.6	—
19	3	Tonsillar diphtheria.....	15,000	30	0.6 × 0.6	—
20	5	Tonsillar diphtheria.....	20,000	31	—	0.4 × 0.8
21	2	Tonsillar diphtheria.....	35,000	31	—	—
22	2	Tonsillar diphtheria.....	15,000	31	0.6 × 1	—
23	3	Tonsillar diphtheria.....	10,000	37	0.6 × 1	0.5 × 0.5
24	9	Tonsillar diphtheria.....	30,000	47	1.5 × 1.5	—
25	7	Nasal diphtheria.....	60,000	48	1 × 1	—
26	3	Nasal diphtheria.....	35,000	45	1 × 1	1 × 1
27	11	Tonsillar diphtheria.....	60,000	54	0.6 × 0.6	—
28	9	Nasal diphtheria.....	20,000	61	1.2 × 1.5	—

As shown in Table 2, about 82 per cent. of children convalescent from diphtheria after receiving large injections of immune antitoxin reacted positively to the diphtherin test; this proportion of positive reactions was about 10 per cent. higher than found among normal children of the same age and probably indicates the development of sensitization to diphtheria protein among these infected individuals.

As shown in Table 3, the prophylactic administration of antitoxin to thirty-three normal children did not influence the percentage of positive diphtherin reactions as tested at the intervals indicated.

TABLE 3.—THE DIPHTHERIN AND TOXIN SKIN REACTIONS IN CHILDREN WHO HAD RECEIVED 1,250 UNITS OF ANTITOXIN

Number	Age, Years	Days after Antitoxin	Reactions	
			Diphtherin, Gm.	Toxin, Gm.
1	3	7	—	—
2	5	10	1 × 1	1 × 1
3	2	10	—	—
4	7	11	0.6 × 1	—
5	4	15	—	0.5 × 0.5
6	1	19	0.6 × 1	—
7	7 mos.	23	1 × 1	—
8	9	25	—	—
9	11	28	—	0.6 × 0.6
10	8 mos.	36	—	—
11	9	37	0.5 × 0.5	—
12	7	48	—	—
13	1½	60	—	1 × 1
14	6	72	1 × 1	—
15	6½	72	—	—
16	3	72	0.6 × 0.6	—
17	7	72	1 × 0.6	—
18	6	72	1 × 0.8	0.6 × 0.6
19	5	72	0.6 × 0.6	—
20	5	72	1 × 1	1 × 0.4
21	4	72	—	—
22	8	72	1 × 1	—
23	9	72	1 × 1	0.5 × 0.5
24	8	72	1 × 1.2	—
25	5	72	1 × 1.5	—
26	2½	72	—	—
27	2	72	0.6 × 0.6	1 × 0.6
28	5	72	—	—
29	2	90	—	—
30	9	90	1 × 1.2	1 × 1
31	6	95	—	—
32	3	120	—	—
33	3	120	1 × 1	1 × 1

DIPHTHERIA BACILLUS CARRIERS AND THE DIPHTHERIN REACTION

As reported in our previous paper, we have found no relation between the Schick toxin reaction and the percentage of diphtheria bacilli carriers. Persons may carry virulent bacilli in the upper air passages and react negatively to the toxin test, the absence of both symptoms of intoxication and local skin reactions being due apparently to the presence of natural antitoxin. Large numbers of carriers have been found who reacted positively to the toxin skin test, but the bacilli proved nonvirulent for guinea-pigs. As shown by Park, however, the Schick test possesses some diagnostic value in a negative way for diphtheria, in that a person presenting certain symptoms, such as a dirty nasal discharge, who reacts negatively to the skin test, may be excluded on the basis that antitoxin in the blood serum sufficient to effect neutralization of the test toxin will protect the individual against diphtheria toxin; on the other hand, a positive reaction indicates that diphtheria may be present, on the basis that the person is shown to be at least susceptible to the toxin.

Similar results were observed with the diphtherin reaction. During this study, cultures were made of the throats of 124 and the noses of twenty-seven persons, in whom both the diphtherin and toxin tests were made, with the following results:

1. Of twenty-six persons convalescent from diphtheria and harboring bacilli virulent for guinea-pigs in the throat, twenty, or 80 per cent., reacted positively to the diphtherin test and twenty-two, or 84 per cent., negatively to the toxin test. In all but one instance the positive toxin tests occurred among persons showing positive diphtherin reactions.

2. The results of the remainder of these tests are summarized in Table 4. None of these cultures was tested for virulence; the majority were of the long and solid types of diphtheria bacilli. The throats of all persons appeared normal, although many of the children had rhinitis, with discharges of varying degrees of severity.

TABLE 4.—THE RESULTS OF CULTURES OF THE NOSES AND THROATS AND OF THE DIPHTHERIN AND TOXIN TESTS

Culture from	Total	Results of Culture	Diphtherin Test		Toxin Test	
			+	—	+	—
Throat.....	19	Positive	9	10	6	13
Throat.....	105	Negative	70	35	32	73
Nose.....	17	Positive	10	7	7	10
Nose.....	10	Negative	7	2	2	8

It is apparent that there is no relation between the occurrence of the diphtherin reaction and the presence of diphtheria bacilli on the mucous membrane of the upper respiratory tract. If these reactions to diphtherin may be interpreted as indicating sensitization to the diphtheria protein, it is possible that sensitization had occurred at a previous time when the mucous membranes harbored the bacilli, or the condition may apparently be acquired by inheritance, the problem being as difficult and indefinite as that surrounding the question why certain persons possess natural diphtheria antitoxin while others do not.

Persons may harbor virulent toxin-producing bacilli and show no evidences of toxemia and react in a negative manner in the toxin test. Their immunity is evidently antitoxic, and while they are not infected in the sense of showing the clinical evidences of diphtheria, they are carriers of dangerous bacilli and may truly be regarded as infected individuals. In this manner the physician may be misled by a negative Schick reaction; the evidence of the test may be taken as an indication that the administration of antitoxin is not required, but nothing more; the question of quarantine because of the possibility of such a person being a carrier of dangerous bacilli must be decided by bacteriologic examination, and preferably by animal inoculation tests.

CLINICAL SIGNIFICANCE OF THE DIPHTHERIN REACTION

If there was sufficient experimental evidence to the effect that cutaneous anaphylactic reactions may be taken as an index to immunity, on the basis that the same or similar antibodies that are capable of reacting with the protein of the dead bacilli may attack the protein and destroy the living bacilli, the diphtherin reaction might prove of some value in the practical management of diphtheria, on the assumption that a person may be protected by the presence of an antibody other than antitoxin.

I have continued this work to determine this point more specifically, in so far as the question can be answered by tests *in vitro* for bactericidal and other antibodies, the results being given in a separate communication;⁴ here it may be stated that the results of these investigations have shown that there is absolutely no relation between the skin reaction and the presence or absence of bacteriolysin and antitoxin for the diphtheria bacillus and its toxins in the body fluids. As far as I am able to determine experimentally, the diphtherin test shows that a person is or is not hypersensitive or anaphylactic to the diphtheria protein, and the chief clinical significance of this reaction consists almost solely in the fact that these reactions, when occurring during the application of the Schick test, may be regarded as positive toxin

4. Kolmer, J. A.: The Diphtherin Skin Reaction in Relation to Immunity in Diphtheria, *Journal of Immunology*.

reactions and accordingly followed by needless attempts at passive or active immunization. My experiments show that immunity in diphtheria is practically solely antitoxic in character, and the Schick test appears to fulfil the requirements of a practical test for immunity to this infection.

Furthermore, as indicating the absence of any relation between the anaphylactic diphtherin test and resistance in diphtheria, I have seen three persons yielding positive diphtherin reactions contract diphtheria; all of these had likewise yielded positive toxin reactions, indicating thereby an absence of sufficient natural antitoxin to confer immunity to this infection.

As far as I am aware, the chief practical value of the diphtherin reaction, entirely aside from its theoretical and academic interest, is as a control on the Schick test to detect and differentiate the anaphylactic from the true toxin reaction.⁵

CONCLUSIONS

1. Following the injection of diphtheria toxin in the conduct of the Schick test for antitoxic immunity in diphtheria, inflammatory reactions may be produced (1) by trauma and undue sensitiveness of the skin; the influence of these reactions may be minimized by injecting a minimum quantity of fluid (not over 0.1 c.c.); by using a stock toxin of high potency in order to require high dilution and the consequent injection of a minimum amount of the constituents of the broth, and by the employment of a proper technic (especially a small needle); (2) by an anaphylactic reaction to the protein of the diphtheria bacillus and to a lesser extent to the protein constituents of the broth itself, the former being more important; (3) by the irritating effects of the toxin itself, constituting the true toxin reaction of Schick.

2. An anaphylactic skin reaction to the protein of the diphtheria bacillus was observed in about 70 per cent. of children and 35 per cent. of adults following the intracutaneous injection of a polyvalent antigen of washed, neutralized and heat-killed diphtheria bacilli (diphtherin).

3. These reactions were regarded as anaphylactic in character and therefore entirely distinct from the true toxin reaction of Schick.

4. The percentage of positive diphtherin reactions was higher than the anaphylactic reactions observed with the toxin of the Schick test due to a higher amount of protein being injected.

5. Lately Zingher (*The Pseudoreaction in the Schick Test and Its Control*, Jour. Am. Med. Assn., 1916, lxvi, 1617) has advocated for this purpose the injection of a toxin heated at 75 C. for five minutes to destroy the toxin or one overneutralized with antitoxin. I have tried both methods and am ready to subscribe to the value of the former as fulfilling all the requirements for detecting the anaphylactic state under conditions governing the conduct of the toxin test.

5. About 53 per cent. of persons of various ages yielded positive diphtherin and negative toxin (Schick) reactions. About 10 per cent. yielded negative diphtherin and positive toxin reactions, both tests agreeing therefore in about 63 per cent. of persons; 12.5 per cent. reacted positively and 24.1 per cent. negatively to both tests.

6. The percentage of positive diphtherin reactions was slightly greater among those who were convalescent from diphtheria.

7. There is no relation between the occurrence of positive and negative diphtherin and toxin reactions and the presence or absence of diphtheria bacilli in the upper air passages. A negative toxin reaction (Schick) in a person presenting clinical evidences of infection indicates that the individual does not require antitoxin, but nothing more; he may be infected with virulent diphtheria bacilli capable of disseminating the disease.

8. While the diphtherin test indicates hypersensitiveness to the protein of the diphtheria bacillus, it has probably no value as an index of immunity and is of practical interest mainly from the viewpoint that the anaphylactic reaction may be mistaken for a positive Schick reaction.

CLINICAL DEPARTMENT

SARCOMA OF THE KIDNEY TREATED BY THE ROENTGEN RAY*

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It is generally accepted as axiomatic that the only hope in cases of sarcoma of the kidney in childhood lies in early nephrectomy. Even under this procedure the mortality is very high on account of the likelihood of metastases, although the operation itself may be well borne.

The following case is reported because the growth was so large that no surgeon was willing to undertake its removal. For this reason recourse was had to treatment by the Roentgen ray. For a time there was marked improvement. The tumor became much smaller in size, and the child gained in weight and strength. After a time, however, the tumor began to increase in size again. Later, the child contracted measles, with complicating bronchopneumonia. At necropsy the actual results of the Roentgen ray treatment on the tumor mass could be studied. The report herewith submitted is presented because of the opportunity offered to study the effects of intensive Roentgen-ray treatment in a case of this sort.

W. S., boy, white, aged 4 years, was admitted to the pediatric service of the Cincinnati General Hospital on Oct. 20, 1915. The history was one of increasing languor and lassitude, with loss of appetite and anemia. The mother had noticed a mass in the abdomen three months before the child was brought to the hospital. A physician outside had suggested Roentgen-ray treatments. Two of these were given by a roentgenologist. After each of these treatments the boy vomited and passed almost pure blood for a day. This statement by the mother was later confirmed by the roentgenologist himself. For a time after the treatments the boy seemed better, but the improvement did not last.

On examination the child was found to be poorly nourished. Except for the condition of the abdomen, the physical findings were not of moment.

The entire left abdomen was filled by a tumor mass, extending from the costal margin in the nipple line to 3 cm. above the symphysis. The tumor extended 1 cm. to the left of the umbilicus. It was hard, distinctly nodular, apparently not tender to pressure and could be moved forward by pressure from behind.

Urinalysis on admission showed distinct microscopic hematuria. The blood showed a secondary anemia. Fluoroscopic examination with colon partly filled with gas showed a sharply defined dark shadow in the region normally occupied by the kidney. Roentgen-ray plate of the lungs for the characteristic metastatic sarcomatous shadows was negative.

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In view of the fact that all of the surgeons who saw the child advised against operation because of the apparent hopelessness of the case, Roentgen-ray treatments were instituted.

Treatments were given with the Coolidge tube. Three areas, front, back and side of the tumor, were covered at each treatment, except the first and second, when one and two areas, respectively, were treated. Twenty treatments were given at intervals of about a week, with a dosage as indicated in the table. The distance in all treatments was 8 inches, with a spark gap of 9 inches.

TABLE 1.—DOSAGE EMPLOYED IN ROENTGEN-RAY TREATMENTS

Date	Ma. Seconds
1915—	
Oct. 30.....	10
Nov. 5.....	15
Nov. 9.....	15
Nov. 15.....	20
Nov. 23.....	25
Dec. 1.....	25
Dec. 8.....	25
Dec. 15.....	25
Dec. 24.....	25
Dec. 29.....	25
1916—	
Jan. 4.....	25
Jan. 12.....	25
Jan. 19.....	25
Jan. 26.....	25
Feb. 5.....	25
Feb. 12.....	25
Feb. 21.....	25
March 3.....	50
March 10.....	50
March 17.....	50

Before each Roentgen-ray treatment the child was given full doses of potassium citrate for a day. As a result of this alkalinization, no Roentgen-ray toxemia followed any of the treatments, except the last. Neither was there any increase of the blood in the urine after the treatments.

After the seventh treatment, given on December 8, it was noted that the tumor had decreased very markedly in size. The child had gained several pounds in weight, looked rosy and well and played like an apparently normal child. In January the child had an attack of influenza, then epidemic in the wards, with double otitis media. The recovery was prompt. By March 1 the child was again very listless and apathetic. The tumor had grown appreciably in size. On March 30 the boy came down with measles, and death occurred on April 4.

The necropsy showed a sarcoma of the left kidney with small metastasis in both lungs and in the liver. The complete pathologic report is not given here.

At my request Prof. P. G. Woolley, pathologist to the hospital, made a microscopic examination of the tumor itself, with reference to the effects of the Roentgen ray on the growth. His report is herewith submitted:

Specimens for microscopic examination were removed from five different points in the tumor, one from near the upper pole, one from near the lower

pole, one from the middle of the tumor at the edge of a hemorrhagic area, and the other two from intermediate portions. The capsule of the tumor was thick and hyaline like that seen in *Zuckergussleber*.

The stained sections showed the most widespread and generally diffuse necrotic changes, with no evidence of inflammatory reaction. Even the stroma showed degenerative changes, associated with irregular areas of edema. The parenchyma was almost completely necrotic, and, except in a few areas, chiefly near the lower pole, showed almost no evidence of structure. One could discern the remains of stroma and parenchyma, by means of the staining reactions, but all histologic cellular structures were lost. Karyorrhexis and karyolysis were obvious and the general appearances suggested those seen in areas of diffuse caseation. The capsule of the whole tumor mass was, on the other hand, hyaline, and, especially about the blood vessels, showed the structure of hyaline connective tissue. At no place was there any evidence of malignant cellular infiltration.

In the areas where some tumor structure persisted, the appearances were those of an alveolar sarcoma, and in these areas short spindle cells and round cells were present, chiefly the latter. In these areas the capillary vessels were healthy. About the margins of these tumorous foci the tumor cells and the interstitial cells were both changed. The former showed, first, pyknosis, and, as the areas of complete degeneration were approached, rhexis and swelling; the latter, edema and vacuolization.

The fact that the whole necrotic process was so widespread in such a large tumor mass; that there was no evidence of vascular thrombosis in the main vessels and no evidence of infarction; and that the degenerative process appeared to be a gradually progressive one, indicates that the Roentgen-ray treatments were at least partially the cause of the retrogression.

In view of some recently reported cases of hypernephromas of the kidney cured by the Roentgen ray it has seemed worth while to put on record this failure of the treatment in a sarcoma of the kidney in childhood.

Yet it should not be forgotten that the case was a particularly unfavorable one. Unquestionably, when a nephrectomy can be done with any prospect of success, it should be the procedure of choice. But it must be remembered that the mortality under surgical procedure is very high.

In view of the changes effected in the tumor mass by the Roentgen ray in this case (and the fact being admitted that one case does not permit the drawing of any sweeping conclusions), it seems justifiable to say that if nephrectomy is contraindicated in a case of sarcoma of the kidney, the Roentgen ray should be given a thorough trial.

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PROGRESS IN PEDIATRICS

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THE PROTEIN METABOLISM OF AN INFANT *

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The diversity of opinion among pediatricians concerning the digestion of protein has led to much discussion, and although certain phases of the question have been cleared up, there still remains much to explain. Recently Mendel and his co-workers have attacked the problem from a new angle in their brilliant studies in growth and the part played by the various members of the protein group in affording a "growth impulse" in growing animals. Studies of the effect of protein on the energy metabolism of infants have been carried on in Professor Lusk's laboratories at Cornell University Medical College by Howland¹ and more recently Hoobler and Murlin² have added much to our knowledge of this phase of the subject.

Although clinical symptoms of protein indigestion have been recognized by many clinicians, mainly of the American schools, an equally large number maintain that protein is harmless even in large amounts. The two groups may be roughly divided into those who use raw milk in infant feeding on the one hand, and those who use principally boiled or heated milk on the other hand. The question of the age of the infant also plays a part in the quantity of protein that may be given without resulting in symptoms of indigestion. It may be said, in general, the younger the infant is, the more frequently do symptoms of indigestion appear when large doses of protein are given. After the age of 5 or 6 months, the danger of giving an average infant more protein than it can tolerate diminishes rapidly. Exceptions, however, may be found in the abnormally strong and vigorous infant who can digest more, or the weak infant who can digest relatively less, at a given age. A third factor which seems to influence the ability of the infant to digest protein is presence of disease in the intestines. That

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* From the Children's Medical Department of the Massachusetts General Hospital.

1. Howland: Tr. Fifteenth Internat. Cong. Hyg. and Demog., 1912, ii, 438.

2. Murlin and Hoobler: AM. JOUR. DIS. CHILD., 1915, ix, 81. Hoobler: AM. JOUR. DIS. CHILD., 1915, x, 153.

is not confined to protein alone, but applies to all the other food elements. Finally, clinical symptoms of indigestion which apparently are the result of too much protein in the food are not so common as those which are brought about by an excess of carbohydrates or fat in the food. These symptoms depend in part on whether the milk is raw or sterilized. Since the only definite outward signs of protein indigestion are casein curds in the stools, and since boiling the milk causes these curds to disappear from the stools,³ casein curds are rarely seen in communities which sterilize all their milk, and the diagnosis of protein indigestion is made more difficult than ever.

Selter⁴ described a picture of intoxication from protein in which there was an excursion of body temperature from 37 C. (98.6 F.) to 34 C. (93.2 F.) (subnormal), slow pulse and superficial respiration. The color of the skin became bluish gray. He found that the urine contained a kenotoxin which, when injected into mice, resulted in symptoms similar to those which he described in babies. Hoobler⁵ subsequently found that when a large amount of protein was given to an infant, "the child no longer took interest in his surroundings, and gradually entered into a state of semistupor. The pulse was slower and there were times when the respirations were slightly irregular. The stupor continued for a few days after the observations ceased," after which "it gradually lessened, so that within one week the child was normal again and began to gain weight." Monrad⁶ and Morse⁷ believe that casein is not harmless and may cause indigestion, while Salge⁸ speaks of a condition in which he is unable to give specific clinical symptoms, as *Eiweissnahr Schaden*. Holt and Levene⁹ observed a rise in temperature in five instances during the administration of a "synthetic food" containing 6 per cent. of casein, and a retention of chlorids for three or four days preceding the rise in temperature. They draw attention to the similar rise in temperature described by Vaughan after the parenteral injection of protein. Finkelstein and his followers, on the other hand, believe that casein is harmless, while Howland¹⁰ and others say that casein curds in the stools are of "limited, if any, pathological importance, but rather depend on physical conditions in the gastro-intestinal tract."

3. Brennehan: AM. JOUR. DIS. CHILD., 1911, i, 341. Ibrahim: Monatschr. f. Kinderh., 1911, x, 55.

4. Selter: Deutsch. med. Wchnschr., 1908, p. 512.

5. Hoobler: Footnote 2, second reference.

6. Monrad: Monatschr. f. Kinderh., 1911, x, 244.

7. Morse: New York Med. Jour., 1913, xcvi, 477.

8. Salge: Ztschr. f. Kinderh., 1912, 112.

9. Holt and Levene: Med. Klin., 1913, ix, 258.

10. Howland: AM. JOUR. DIS. CHILD., 1913, v, 390.

An analysis of the figures of previous investigators does not give any explanation of the clinical symptoms which are seen in practice, and it was with the hope of answering some of the clinical questions that this investigation was undertaken. Although the figures obtained do not answer any questions from the point of view of the clinician, they contain many interesting facts which will be commented on later, and serve to substantiate or amplify the findings of previous investigators. We believe that they are of sufficient importance to record.

F. W. L. was born Dec. 4, 1913, at full term. During the first three months of life he was fed on modified milk. On March 12, 1914, he came to the outpatient department of the Massachusetts General Hospital with colic and

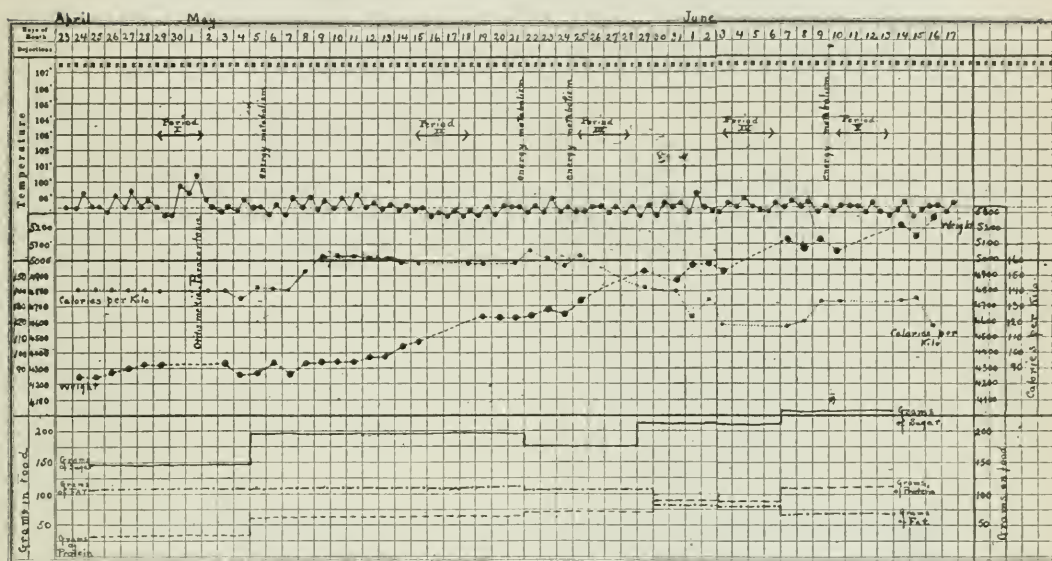


Fig. 1.—Metabolism record of F. W. L., covering a period of nearly two months, showing the intake of fat, protein and sugar from day to day, its value in calories per kilogram of body weight, the increase in weight of the infant and the variation in body temperature.

constipation, and weighing 4,280 gm. His formula was changed from time to time, the last one being fat 2.5, lactose 6, protein 1.6, 4 ounces, 7 feedings. Just before entering the children's ward, April 23, 1914, at the age of 4½ months, he weighed 4,315 gm. Physical examination showed that he was poorly developed and poorly nourished with flabby musculature, but was otherwise normal, the only fact worthy of note being that the liver dulness extended from the fourth intercostal space to 3 cm. below the edge of the ribs in the nipple line. Figure 1 shows the temperature, weight curves, calories and food per twenty-four hours, given during the time he was in the hospital, and at the different periods investigated. The periods in which the food and excreta were examined were each of three days' duration, the stools at the beginning and end of each period were marked off with charcoal. In one instance the food was changed twenty-four hours before the period commenced, and

in all others several days had elapsed after the food was changed and before the period was commenced. The urine and stools were collected in the manner described by one of us,¹¹ and it was frequently noted that the baby was perfectly comfortable during the periods of investigation. Figure 1 shows that during the entire period the baby was in the hospital he gained from 4,280 gm., his weight on entrance, to 5,275 gm., his weight on discharge, June 16.

The periods were arranged so far as possible so that he would receive the same number of calories per kilogram of body weight per day. The amount of protein was increased in each successive period so that during the last period he was offered over three times as much as he had during the first period. During the last period the baby refused to take all the food offered him, thus reducing the protein intake. The milk used in mixing the formulas was raw. The writers believe that boiling the milk might have modified the results obtained.

TABLE 1.—TOTAL FIGURES FOR EACH THREE-DAY—

Period	Age, Mo.	Weight		Food							Urine	
		Start, Kg.	End, Kg.	Calo-ries per 24 Hr.	Calo-ries per Kg.	Fat, Gm.	Sugar, Gm.	Pro-tein, Gm.	Nitro-gen, Gm.	Ash, Gm.	Nitro-gen, Gm.	Ash, Gm.
1	5¼	4.3	4.335	527	122	106	143	31	4.79	9.26	2.876	2.37
2	5¾	4.415	4.65	650	143	107	196	60	9.31	11.33	5.816	5.02
3	6	4.66	4.936	626	130	102	176	70	11.06	18.3	7.482	6.69
4	6½	4.93	5.17	649	130	84	217	89	13.91	21.6	8.065	7.4
5	6¾	5.05	5.235	623	123	64	233	109	17.01	27.66	11.893	13.87

Table 1 shows the total amount of calories, fat, sugar, protein, nitrogen and ash ingested for each period of three days, and the amount excreted in the urine and stools.

It was found that in Period 1 the baby was hungry, even though he was receiving 122 calories per kilogram of body weight. The investigations of Benedict and Talbot¹² have shown that the more a baby is underweight the greater will its basal heat production be per kilogram of body weight per twenty-four hours. It is not surprising then that it was necessary to give the baby more than 120 calories because he weighed less than the average weight for his age (4,300 gm. against the average weight of 6,800 gm.). The amount of food, therefore, was increased until the baby was satisfied in the second period. From this time on he received approximately the same total number of

11. Talbot: Apparatus for Metabolism Experiments in Male Infants, Jour. Am. Med. Assn., 1909, liii, 1818.

12. Morse and Talbot: Discussion of Benedict and Talbot, Dis. Nutrition and Infant Feeding, New York, 1915, p. 56.

calories in twenty-four hours. The calories per kilogram of body weight gradually fell as his weight increased, and it was necessary to vary the fat and sugar (lactose) in order to compensate for the increasing amount of protein given. Since the ash is principally in the protein of the milk, the ash increased as the protein increased.

Folin's¹³ investigations on the adult showed that if a man ingested a diet containing a medium amount of protein, and again one nearly free from protein, the difference in amount of total nitrogen in the urine in the two instances was due almost exclusively to a difference in the output of urea. The quantity of creatinin eliminated remains independent of the quantity of protein metabolized, provided the diet is practically creatin free, as Folin's were, the protein being supplied from milk. The same is less strikingly true of uric acid. This led Folin to distinguish between an endogenous, or repair, protein metabol-

—PERIOD; DETAILED ANALYSIS OF URINE NOT INCLUDED

Nitro- gen,	Ash, Gm.	Total Fat, Gm.	Stool					Nitro- gen Bal- ance, Gm.	Fat Util- ized, per Cent.	Ash Bal- ance, Gm.	Weight Bal- ance, Gm.
			Neut- ral Fat, Gm.	Fatty Acids and Soaps, Gm.	NH ₃ Nitro- gen, Gm.	NH ₃ Nitro. in % Total N	Titra- ble Acid, Gm.				
0.895	4.21	19.16	0	19.16	0.087	9.7	51	1.02+	82	2.68+	35+
1.28	7.4	12.1	0.32	11.78	0.16	12.5	82	2.21+	89	1.09—	235+
1.475	7.84	8.42	0	8.52	0.12	8.1	42	2.10+	91	2.76+	276+
1.92	8.53	14.9	1.34	13.56	0.183	6.4	96	3.92+	88	5.67+	240+
3.477	12.08	12.37	1.03	11.34	0.254	7.3	194	1.64+	81	1.71+	180+

ism, and an exogenous, or energy, protein metabolism. That is, the term "endogenous" metabolism is used for the chemical processes which are concerned in maintaining the chemical structure of the cell protoplasm, in contrast to the processes of combustion, which the cell carries on for the purpose of using the resulting energy in accomplishing its physiologic functions. Creatinin and uric acid are regarded as being produced solely by endogenous metabolism. Probably some ammonia and urea are also produced by the processes of repair metabolism, but in the main ammonia and urea together represent the extent of the combustion of protein, for the sake of its energy content, and will depend on the amount left over after the cell protoplasm has supplied its structural needs. The absolute amount of ammonia appearing in the urine, is, as shown by Henderson and Palmer,¹⁴ a measure of the extent to which this organic base is being used to maintain the nor-

13. Folin: *Am. Jour. Physiol.*, 1905, xiii, 117.

14. Henderson and Palmer: *Jour. Biol. Chem.*, 1914, xvii, 305.

mal reaction of the blood. The ammonia is available for this purpose at the expense of the neutral substance, urea.

If Folin's views are accepted, we may expect that since the process of cell repair probably goes on at a fairly constant pace in a normal

TABLE 2.—DAY TO DAY DETERMINATIONS FOR ACID FACTORS, NITROGEN—
THREE-DAY PERIODS WITH—

Period	Protein in Food, Gm.	24-Hour Amount Urine, C.c.	Acid Excretion					Nitrogen, Mg.		
			+ (H)	Titra- ble Acid, C.c., N/10	NH ₃ C.c., N/10	Total Acid, C.c., N/10	A/NH ₃	Total Nitro- gen	Urea N	NH ₃ N
1	10.5	720	5.9	54	127	181	0.43	966	669	178
	9.9	815	5.3	84	170	254	0.5	966	624	238
	10.2	750	6	60	121	181	0.5	944	688	170
2	20.7	740	5.9	57	114	171	0.5	2,062	1,717	159
	19.1	775	6.4	55	116	171	0.47	1,842	1,614	163
	19.5	900	5.9	52	105	157	0.5	1,912	1,548	147
3	24.5	840	6.7	48	107	155	0.45	2,632	2,234	148
	24.6	760	6.7	48	131	179	0.37	2,470	2,039	183
	21.3	740	6.2	63	139	202	0.45	2,380	1,944	194
4	29.1	600	2,205
	28.1	790	3,000
	31.4	805	2,860
5	35.8	850	3,871
	35.3	700	3,942
	37.4	900	4,080

TABLE 3.—SUMMARY FROM TABLE 2; FIGURES ARE FOR—
RESULTS FOR THE THREE—

Period	Protein in Food, Gm.	Amount Urine, C.c.	Acid Excretion					Nitrogen, Mg.		
			+ (H)	Titra- ble Acid, C.c., N/10	NH ₃ C.c., N/10	Total Acid, C.c., N/10	A/NH ₃	Total Nitro- gen	Urea N	NH ₃ N
1	10.2	762	5.8	66	139	205	0.47	959	660	195
2	20.0	805	6.1	55	112	166	0.49	1,939	1,626	156
3	23.3	780	6.5	53	126	179	0.42	2,494	2,072	175
4	29.5	732	2,688
5	36.2	817	3,964

individual, the end products of endogenous metabolism will be constant in the absolute amount and unaffected by the varying amount of protein in the diet, whereas, the total urea plus ammonia nitrogen will vary directly with the protein intake. As there is no known organ in

the body in which protein is stored, the surplus protein (after cell repair and growth in infants have been supplied) must be burned.

Table 1 shows the total figures for each three-day period. During each period the baby gained rapidly in weight with the exception of

—AND SULPHUR PARTITION, PHOSPHATES AND CHLORIDS IN URINE FOR FIVE
—INCREASING PROTEIN INTAKE

Nitrogen, Mg.					Sulphur, Mg. SO ₃				Phos- phates, Mg. P ₂ O ₅	Chlorids, Mg.
Creat- inin N	Crea- tin N	Uric Acid N	Un- deter- mined N	Per Cent. of Food N in Urine	Total	Inor- ganic	Eth- ereal	Neut- ral		
25	1	32	61	59	174	95	29	50	360	350
25	3	31	41	62	200	121	..	44	540	770
19	4	33	30	59	202	118	26	58	500	90
20	13	11	150	64	363	269	14	81	520	520
19	11	10	25	61	338	246	18	73	550	570
20	11	13	173	62	317	239	12	67	420	560
22	28	19	181	64	429	362	14	54	550	600
21	29	17	181	59	433	361	16	57	540	830
22	22	17	191	66	420	366	10	45	600	1,130
20	25	48	385	318	13	54	660	690
22	28	68	509	423	17	69	730	1,680
20	22	58	501	421	15	65	720	1,340
25	39	69	672	594	12	65	940	1,800
22	40	71	679	588	20	71	920	1,800
23	39	70	680	595	22	70	950	1,800

—TWENTY-FOUR HOUR AMOUNTS OBTAINED BY AVERAGING THE
—SUCCESSIVE DAYS OF EACH PERIOD

Nitrogen, Mg.				Sulphur, Mg. SO ₃				Phos- phates, Mg. P ₂ O ₅	Chlorids, Mg.
Creat- inin N	Crea- tin N	Uric Acid N	Un- deter- mined N	Total	Inor- ganic	Eth- ereal	Neutral		
23	3	32	44	190	111	28	51	467	403
20	12	11	116	344	255	15	74	497	550
22	26	18	184	428	363	13	52	563	853
21	23	465	387	15	63	703	1,237
23	39	679	592	18	69	937	1,800

Period 1, in which he received the minimum amount of protein and fewer calories than during any other period. He was hungry after each feeding, and, therefore, the amount of food was increased until he was satisfied. During the remaining periods he was satisfied and

happy. The increase of nitrogen in the food was accompanied by a regular increase of the total nitrogen in the urine. This corresponds with the findings both in the infant and in the adult. There was an increase of ash in both the urine and the stools as the protein or nitrogen in the food was increased, and there was more ash in the stool than in the urine in all periods except Period 5, in which slightly more was excreted through the urinary tract than through the gastro-intestinal tract. The increasing amount of ash in the food did not affect its mode of exit from the body. There was, however, a marked increase in the titrable acidity of the stools in the last period, and a larger amount of sugar in the food during this period, which may have had some causative relation to these findings.

TABLE 4.—AMOUNT OF ETHEREAL SULPHATES IN URINE WITH AN INCREASING AMOUNT OF AMMONIA IN THE STOOL; FIGURES ARE FOR TWENTY-FOUR-HOUR AMOUNTS

Period	Protein per Kg. in Food, Gm.	NH ₃ N in Stool, Gm.	Total Sulphur in Urine, Mg. SO ₃	Ethereal Sulphates, Mg. SO ₃		
				Total	Per Kg.	Percentage Total Sulphur
1	2.3	29	190	23	6.5	14.7
2	4.4	53	344	15	3.3	4.4
3	4.8	40	428	13	2.7	3
4	5.9	61	465	15	3.0	3.2
5	7.1	85	679	18	3.6	2.6

The retention of nitrogen (nitrogen balance) increased with the increase of nitrogen in the food up to the last period, when the baby refused to take all the food that was offered him, and, clinically, seemed to be on the verge of a digestive upset. In this period there was a marked diminution of the retention of nitrogen and a great increase in the nitrogen in the stools. During the last two periods there were casein curds in the stools, a very few in the fourth period, when there was a slight increase in the stool nitrogen, and many in the fifth period, when there was a great increase in the stool nitrogen. In the latter instance they made up 15 per cent. of the total fecal nitrogen.¹⁵ Coincidentally there was a decrease in the retention of ash. (We are unable to explain the negative ash balance in Period 2.) These figures make one speculate as to what might have happened if a further increase of protein had been persisted in. The

15. The stools during the other periods were remarkably uniform in quality. They were light yellow or yellow, of smooth salve-like consistency, never stiff. They were normal in all respects except that they were quite a bit larger than the usual twenty-four hour stool.

figures of the utilization of fat do not indicate that the fat digestion was influenced to any great degree by the changes made in the food.

Table 2 shows the day to day determinations for acid factors, nitrogen and sulphur partition, phosphates and chlorids in the urine for each of the five three-day periods.

Table 3, which is a summary of Table 2, shows that the amount of ammonia excreted in the urine is closely in proportion to the titrable acid in the urine. Henderson and Palmer¹⁴ find in adults with normal kidneys that titrable acidity divided by the ammonia gives a fairly constant ratio of 0.75 in average, regardless of the amount of protein in the diet. The ratio titrable acidity divided by the ammonia in our

TABLE 5.—CREATININ, URIC ACID, ETHEREAL SULPHATES AND NEUTRAL SULPHUR PER KILOGRAM BODY WEIGHT WITH INCREASING PROTEIN INTAKE; FIGURES FOR TWENTY-FOUR-HOUR AMOUNTS

Protein per Kg. in Food, Gm.	Creatinin N per Kg., Mg.	Uric Acid N per Kg., Mg.	Ethereal Sulphates per Kg., Mg. SO ₃	Neutral Sulphur per Kg., Mg. SO ₃
2.3	5.3	7.4	6.5	11.8
4.4	4.4	2.4	3.3	16.3
4.8	4.6	3.8	2.7	10.8
5.9	4.2	...	3.0	12.5
7.1	4.5	...	3.6	13.4

first three periods was 0.47, 0.49, and 0.42. One of us, Gamble,¹⁶ found in an investigation carried on at the Boston Floating Hospital that when more than the usual amount of protein was given the A/NH₃ ratio fell, in other words, increasing the protein in the diet resulted in an increase of urinary ammonia out of proportion to its usual relation to the amount of titrable acid. We regret that the acid factors were not determined during the last two periods.

The ammonia coefficient, that is, ammonia nitrogen divided by the total nitrogen for the first three periods, were 20 per cent., 8 per cent., and 7 per cent. The coefficient of 20 per cent. for the first period is very high and might be taken to mean an excess of acid excretion. This, however, is not the case, as is shown by the absolute values for ammonia and titrable acidity, which are practically the same in all three periods. The seemingly high coefficient is due to a low total nitrogen in the urine, because of the low protein intake. Since a high ammonia coefficient is generally taken as evidence of acidosis, it is important to bear in mind that when the food contains only a small

16. Gamble: Not yet published.

amount of protein, a high ammonia coefficient will not necessarily mean acidosis. If, on the other hand, there is an average amount of protein in the diet, a high ammonia coefficient is of greater significance.

The urea nitrogen increased regularly with the amount of nitrogen in the food, as it does in adults, and indicates the extent of the exogenous protein metabolism.

The creatinin in the urine remained extremely constant in the total amount, and independent of the quantity of protein metabolized. It measures the endogenous metabolism of the individual. Previous investigators have found that the excretion of creatin in the urine of man is independent of the amount of protein in the food.

Our figures show that the amount of creatin in the urine of this infant depended on the amount of protein in the food. It increased

TABLE 6.—SUMMARY OF ENERGY—

Date	Body Weight and Surface	Height, Cm.	Age, Mo.	Carbon Dioxid per Hour, Gm.	Respiratory Quotient
5/21/14	4.74 Kg.	60	5½	6.48
	$10.3 \sqrt{w^2} = 0.291 \text{ Sq. M.}$			5.02	0.88
				6.04
5/23/14	4.75 Kg.	60	...	7.94
	$10.3 \sqrt{w^2} = 0.291 \text{ Sq. M.}$			4.72	0.84
				6.53
6/ 9/14	5.12 Kg.	62	6	7.6
	$10.3 \sqrt{w^2} = 0.306 \text{ Sq. M.}$			5.9	0.92

* Periods were of least activity according to the kymograph records.

with the protein as did the urea. It seems likely, therefore, that the creatin in the urine of this infant was a product of his exogenous metabolism.

The uric acid was highest with the lowest protein intake.

The ethereal sulphates, according to Folin, are almost entirely the product of endogenous metabolism. Table 3 shows that in our baby the ethereal sulphates were unaffected by the increase of protein in the food. The inorganic sulphates increased regularly with the increase of protein in the food and are, like urea, a product of exogenous metabolism. The neutral sulphur is, however, roughly constant.

Table 4 shows the amount of ammonia in the stools, which may be taken as an index of intestinal putrefaction. It increased with the increasing protein intake. This substantiates other findings of

Gamble,¹⁷ but does not show any relation between the ethereal sulphates of the urine, which remain absolutely constant, and the stool ammonia. The distinctly larger amount of ethereal sulphates, both total and per kilogram of body weight, in the period with the least ammonia in the stools seems to indicate that indol, phenol, and skatol in the intestinal canal do not contribute much to their formation.

The phosphates and chlorids in the urine increased with the increasing food protein in all five periods, while the undetermined nitrogen increased in like manner in the first three periods (the last two were not determined). It is possible that the undetermined nitrogen contains other products of the exogenous metabolism.

In Table 5 creatinin, uric acid, and the ethereal sulphates, products of the endogenous metabolism, are put on the per kilogram basis

—METABOLISM OF A BOY, F. W. L.

Heat Produced per 24 Hours, Calories		Rectal Temperature C. F.	Average Pulse Rate	Remarks
Per Kg.	Per Sq. Meter (Lissauer)			
..	36.8 (98.2)	127	Formula feeding (6 oz.) about ½ hour before the observa- tion was started
72	1,175*	118	
87	1,412	36.8 (98.2)	127	
..	37.3 (99.2)	138	Formula feeding (5 oz.) about ½ hour before the observa- tion was started
70	1,144*	117	
97	1,584	37.0 (98.6)	130	
..	36.9 (98.4)	142	Formula feeding (6 oz.) about 1 hour before the observa- tion was started
76	1,268*	37.1 (98.8)	137	

because it seems likely that the endogenous metabolism depends on the protoplasmic mass of the individual infant, just as does the total energy metabolism. The interesting point brought out in this table is that whereas the figures remain relatively constant during the last four periods, in the first period in which the protein approaches the minimum protein intake necessary for a nitrogenous equilibrium, there is a definite increase in the excretion of these three bodies, even though there was a small positive nitrogen balance in this period. Can it mean that the level of endogenous metabolism rises as the minimum protein intake necessary for a nitrogenous equilibrium is approached?

17. Gamble: Ammonia and Urea Content of Infants' Stools, *AM. JOUR. DIS. CHILD.*, 1915, ix, 519.

The basal energy metabolism¹⁸ was investigated between Periods 1 and 2, but no periods which could be considered quiet periods were obtained. Between Periods 2 and 3 two separate quiet periods were obtained, and between Periods 4 and 5 one quiet period was obtained. These periods are herewith recorded. Although the small number of periods does not justify any conclusions, it can be seen that the calories per square meter are distinctly higher with the higher protein intake than with the lower protein intake. These findings are, therefore, constant with those published from Lusk's laboratory.

SUMMARY

This work shows that the metabolism of F. W. L. was going on in a normal manner despite the increase of protein in the food. The baby gained weight very rapidly after he received sufficient calories to satisfy his appetite. Since he was considerably below the average weight for the age when the work commenced and gained so much weight during the investigations, the question may be brought up as to whether he falls into a similar class to that occupied by a patient convalescing from typhoid fever. It is impossible to answer this, but clinically he came into the class of babies "doing well."

The level of his metabolism varied because he needed more calories in the beginning, when he was underweight, than at the end, when he more nearly approached the normal weight for his age. During the last period he did not take all the food that was offered him, his natural instincts and appetite protecting him from a food that was ill balanced. This experience makes us speculate as to whether other investigators may not have had the same experience, and, for that reason, found no chemical evidence of a protein disturbance of metabolism. The endogenous metabolism of uric acid, creatinin and ethereal sulphates was maintained on a very constant level, while the exogenous metabolism, namely, urea, creatin, inorganic sulphates and the metabolism of phosphates, chlorids and undetermined nitrogen, increased with the protein in the food. The fat and carbohydrate absorption was within normal limits, although the fat utilization in Periods 1 and 5 was almost outside normal limits. The retention of nitrogen suddenly dropped in the last period, even though there was a greater intake and absorption of nitrogen. This loss was found in the stools, in which casein curds were found in large numbers. The ammonia in the stools increased with the increasing protein intake, and may be considered an index of intestinal putrefaction.

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18. The work was done with the apparatus of the nutrition laboratory of the Carnegie Institution of Washington.

THE BACTERIOLOGY OF THE URINE IN HEALTHY CHILDREN AND THOSE SUFFERING FROM EXTRA-URINARY INFECTIONS *

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The problem of pyelocystitis in infancy and childhood has become more and more important as our knowledge of the frequency of the infection has increased, and the possible serious consequences that it may entail. A few facts regarding pyelocystitis have been pretty well established, namely, that the infection is very much more common in girls than in boys, that the infecting organism is most frequently the *Bacillus coli*, and that the symptomatology of the condition is so indefinite as to make a diagnosis practically entirely dependent on the examination of the urine.

Regarding the mode of infection there seems to be considerable difference of opinion. In practically all articles on the subject, three possible modes of infection are given, namely, (1) ascending infection in the lumen of the urethra; (2) infection by way of the anastomosing lymphatics of large intestines and urinary tract; (3) infection by way of blood stream.

Regarding the third type of infection, the pathologic anatomy of the kidney proves that this type of infection does occur. In like manner the lymphatic route is quite definitely proved. The consensus of opinion in pediatric literature appears to be, however, that the infection by way of the lumen of the urethra is the commonest. The main facts in favor of the urethral route are the predominance of cases in girls, the shortness of the urethra, and the fact that the orifice of the urethra is constantly contaminated with colon bacilli.

Although it may appear that these three facts speak in favor of an ascending infection by way of the lumen of the urethra, nevertheless the question is far from being definitely settled.

In order to get a basis for future work it seemed essential first of all to determine the bacteriology of the normal urine and urethra. It is the object of this paper to record the bacteriologic findings of catheterized specimens of urine taken from thirty girl infants and from thirty-one girls over 2 years of age.

* Submitted for publication June 14, 1916.

* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital.

In an examination of the literature on urinary findings in health practically only a single paper, by Ross,¹ has been found. Ross catheterized nineteen normal children (age not given); of these nineteen specimens, eleven were sterile and eight showed a staphylococcus; of the eight, only three showed staphylococci in the second portion of the urine. Besides these, he catheterized eighty-seven girls the specimens from none of whom were sterile. These contained in forty-three instances pure cultures of colon bacilli, in nineteen the *Bacillus proteus*, and in twenty-five instances a staphylococcus. It was impossible for us to tell from the text how these cases are to me classified, as only three of the colon group did he classify as evident pyelitis and only one in the proteus group. Of the staphylococcus he says, "there is no reason to attach importance to their presence." There are several criticisms to be made of this paper: first, that the urine was incubated for twenty-four hours in liquid mediums and then plated, and second, that the plates were incubated for only forty-eight to seventy-two hours. Under the first point it can be said that one type of organism may easily overgrow other organisms present so as to appear to be present in pure culture, and by the second method of treatment one gets no idea whatsoever as to how many organisms per cubic centimeter there are present in the urine, and it can also be said that many specimens will be sterile at the end of forty-eight to seventy-two hours and yet show a number of colonies at the end of a week.

The technic we employed in obtaining the specimens was as follows: The patient was placed on a table with the limbs widely spread apart, so that the orifice of the urethra was plainly visible. A sterile cotton applicator was now used to thoroughly cleanse the vagina, the external genitalia not being cleansed, while an assistant kept a constant fine stream of 1 per cent. lysol solution playing on the part. The region about the urethral orifice was naturally given special attention. Then with a dry sterile applicator the orifice of the urethra was mopped dry. A sterile catheter was now carefully introduced without touching anything but the orifice. In the infant there is usually a small fold of mucous membrane lying over and covering the urethral orifice, which unquestionably protects the urethra from gross fecal contamination, but makes it almost impossible to avoid touching when introducing the catheter. If by any chance a portion of the vagina other than the orifice was touched a fresh catheter was taken. The urinary samples were collected in two or three sterile tubes, the flow of urine being controlled by compressing a piece of rubber tubing about 2 inches long that was attached to the glass catheter. These samples were labeled

1. Ross: Bacteriology of the Urinary Tract in Children, Lancet, London, 1915, i, 484.

1, 2, and 3, and were cultured separately so as to determine the difference between the first and last urine passed.

One cubic centimeter of urine was used in making the litmus-lactose-agar plates and blood-agar plates, 2 c.c. of urine in the deep dextrose-agar and deep blood-agar tubes. This variety of medium makes identification of the colon group easy, shows the organisms growing only on blood medium, and the deep tubes give opportunity for anaerobic growth. In the course of a few experiments Tubes 2 and 3 were found to be practically identical, so that in the majority of the cultures taken only 1 and 2 were used. Tube 1 was grown in deep dextrose-agar tubes and on a litmus-lactose plate. Tube 2 was grown on a litmus-lactose plate, a blood-agar plate, and in a deep blood-agar tube. In the passage of the catheter through the urethra a certain number of bacteria are carried into the bladder and are washed into the first portion of the urine; so that Specimen 1 represents urethral as well as bladder flora. In order to compare the first and last portion of the urine we have charted the cases as follows designating the first portion as No. 1 and the last as No. 2.

The analysis of Table 2 shows the following:

The chemical and microscopic examination of the urine of the normal cases showed in no instances albumin, the specimens were all acid, a few of them cloudy with urates and phosphates. In a single instance there were a few leukocytes found, in three instances epithelial cells, and in no instance any casts.

Of the twelve normal cases five had sterile urine; of the remaining seven, two had organisms in the first portion of the urine, but none in the second. In one instance No. 1 was sterile when No. 2 contained 2 bacteria per cubic centimeter. In only one instance was a colon-like organism found in this entire series. A single colony of the *Bacillus alkaligenes* developed from 1 c.c. of the first portion of urine in Case 3. Of the remaining five specimens of No. 1 that were not sterile, three showed 1 organism per cubic centimeter and two, 3 organisms per cubic centimeter. No. 2 contained 1 organism per cubic centimeter four times and 2 organisms once. In every instance in which more than 1 organism per cubic centimeter was found there were two types of organism identified.

The examination of the urine of the patients with extra-urinary infections showed very frequently pathologic constituents. The urine was alkaline three times, acid fifteen times. Albumin was present three times. On microscopic examination casts were present three times, a few leukocytes nine times, many leukocytes two times, and red blood corpuscles twice. The two specimens in which many leukocytes and red cells were found contained also a large number of casts, in fact formed a sediment that filled the bottom of the tube for about

one-half inch. A diagnosis of pyelocystitis was made from the microscopic examination of the urine, but cultures did not bear out this finding. The infants were both very acutely ill, and the urine was highly concentrated. This finding emphasized the necessity of care in making a diagnosis of pyelocystitis from a single specimen, even when it is obtained by catheterization.

In Table 3, eighteen cases of extra-urinary infections, there were five instances in which the specimens were sterile. Of the remaining thirteen cases No. 1 was sterile once; in two instances there were 1 or 2 bacteria per cubic centimeter, in two instances from 3 to 5 per cubic centimeter, in two instances from 6 to 10 per cubic centimeter, in four instances from 11 to 20 per cubic centimeter, and in three instances from 21 to 50 per cubic centimeter. In like manner in No. 2 in five instances there was 1 bacterium per cubic centimeter, and in five instances there were from 2 to 5 per cubic centimeter, in one instance 7 per cubic centimeter, and in one instance 13 per cubic centimeter.

An analysis of the six cases in which colonlike organisms were found is shown in Table 1.

TABLE 1.—ANALYSIS OF CASES IN TABLE 3 SHOWING COLONLIKE BACILLI

Case Number	No. 1		No. 2	
	Organisms per C.c.	Gram-Negative Bacilli per C.c.	Organisms per C.c.	Gram-Negative Bacilli per C.c.
13	20	10	1	1
15	6	3	4	2
19	20	10	4	0
24	50+	3	13	0
27	4	2	2	1
29	20	15	4	0

In their relation to the problem of cystitis this group of cases is perhaps the most interesting. Of eighteen cases, six showed the presence of gram-negative bacilli in the first specimens and in one-half of these in the second specimen also. In the second specimen in two instances there was a single organism per cubic centimeter, and in the third, 2 organisms. In each instance the flora of the second represents a dilution of the first, and in all probability represents urethral organisms.

The urines that showed gram-negative bacilli in both No. 1 and No. 2 were from (1) a case of severe atrophy with marked retention of urine, 75 c.c. being obtained on catheterization, the catheter being passed while urine was flowing, No. 1 showing *B. coli* and gram-positive staphylococcus, and No. 2 showing a single colony of *B. coli*;

(2) a case of bronchitis which had in Nos. 1 and 2 *B. enteritidis* and a gram-positive staphylococcus; (3) a case of pneumonia which had in No. 1 and No. 2 a gram-positive staphylococcus and *B. coli*.

Cases 4 and 5 of this series are especially interesting because the catheterized urine in both instances was loaded with pus cells and casts and gave a positive test for albumin, and yet No. 2 in one instance contained only 13 gram-positive staphylococci per cubic centimeter and the other 2 staphylococci and 2 colon bacilli per cubic centimeter. The first of those catheterized at a later date gave a sterile urine, no treatment having been instituted in the meantime. When one considers that in cases of cystitis the urine diluted 1 to 100 million or even 1 to 1 billion usually shows innumerable colonies, the importance of the finding of a single organism per cubic centimeter of undiluted urine is not to be overestimated.

To pass on to the analysis of Tables 3 and 4, it is seen that the normal patients over 2 years of age resemble those below 2 very much in the absence of finding on microscopic and chemical examination. In four cases there were a few leukocytes present and in one instance a positive test for albumin.

In the cases of extra-urinary infections there were only three that showed a positive test for albumin, five with small numbers of leukocytes, one with numerous leukocytes (present in uncentrifuged specimen) and in four instances hyaline casts.

Of the specimens taken from girls above 2 years we find that the number of times sterile urine was obtained in both No. 1 and No. 2 was almost the same as in series 1. In thirteen cases out of thirty-one all cultures remained sterile. The number of bacteria per cubic centimeter in the different urines that showed organisms was very much smaller, however; in only one specimen were there more than five organisms per cubic centimeter. This urine contained twenty-one organisms per cubic centimeter of a long-chained, nonhemolytic streptococcus in pure culture. In only two instances was a gram-negative bacillus found, in both instances the bacillus proteus. In two instances a single colony of the hay bacillus was found. All the remainder were either gram-positive cocci or diphtheroid bacilli. Of the eighteen cases that showed growth in No. 1 or No. 2, in four No. 1 showed no growth; in nine No. 1 showed 1 organism per cubic centimeter; in five No. 1 showed from 2 to 5 organisms per cubic centimeter.

In the eighteen cases No. 2 showed in seven cases no growth; in three cases 1 organism per cubic centimeter; in four cases 2 organisms per cubic centimeter; in one case 4 organisms per cubic centimeter; in one case 21 organisms per cubic centimeter (blood plate).

In this group of thirty-one cases there are only two specimens of urine that contained gram-negative bacilli. These two cases were both

TABLE 4.—URINARY FINDINGS IN—

Case	Age, Yrs.	Diagnosis	Examination of Urine				
			Reac- teria	Albu- min	Cells	Casts	Bac- teria
1	4	Normal.....	Acid	0	0	0	0
2	4	Normal.....	Acid	0	0	0	0
3	5	Normal.....	Acid	0	0	0	0
4	3	Normal.....	Neutral	0	0	0	0
5	5	Normal.....	Acid	0	0	0	0
6	6	Normal.....	Acid	0	0	0	0
7	5	Normal.....	Acid	0	Few mononuclears	0	0
8	5	Normal.....	Acid	+	0	0	0
9	5	Normal.....	Acid	0	Few round cells	0	0
10	5	Normal.....	Acid	0	0	0	0
11	5	Normal.....	Acid	0	Few pus cells	0	0
12	6	Normal.....	Acid	0	0	0	0
13	3	Normal.....	Acid	0	0	0	0
14	3	Normal.....	Acid	0	0	0	0
15	3	Normal.....	Acid	0	0	0	0
16	3	Normal.....	Acid	0	0	0	0
17	5	Normal.....	Acid	0	Few mononuclears	0	0
18	3	Normal.....	Acid	0	0	0	0

TABLE 5.—URINARY FINDINGS IN CASES OF EXTRA-URINARY—

Case	Age, Yrs.	Diagnosis	Temper- ature	Examination of Urine				
				Reac- tion	Albu- min	Cells	Casts	Bac- teria
1	10	Chorea.....	0	Acid	0	Few	0	0
2	11	Chorea.....	0	Acid	0	One group	1 granular and 1 waxy	0
3	10	Chorea.....	0	Acid	0	+ mononuclear and polymorph.	0	0
4	3	Tetany.....	0	Acid	0	0	Few casts and cylinders	0
5	3	Pneumonia.....	0	Acid	0	Few	0	0
6	12	Pneumonia.....	102	Acid	+	Few	+	0
7	11	Chorea.....	0	Acid	0	Few squamous	0	0
8	10	Endocarditis.....	97	Acid	Trace	Few	Hyaline and waxy	0
9	6	Meningitis; bronchitis.....	100	Acid	0	0	Few hyaline and cylindrical	0
10	3	Suspected cystitis.....	*	Acid	0	0	0	0
11	9	No diagnosis.....	103	Acid	0	0	0	0
12	6	Rhinitis.....	102	Acid	0	Pus cells	0	0
13	6	Suspected cystitis.....	0	Acid	0	0	0	0

* Fever for two weeks at a previous time.

—NORMAL GIRLS OVER TWO YEARS OF AGE

Culture No. 1			Culture No. 2		
Number Organisms per C.e.	Number Gram-Negative Bacteria per C.e.	Types of Organism	Number Organisms per C.e.	Number Gram-Negative Bacteria per C.e.	Types of Organism
0	0	0	0	0	0
0	0	0	4	0	Pseudodiphtheroid
0	0	0	0	0	0
0	0	0	21	0	Streptococcus (long chain)
1	0	Gram-positive coccus (short chained)	0	0	0
2	0	Gram-positive diplococcus	2	0	Gram-positive diplococcus
1	0	Gram-positive coccus; hay bacillus	0	0	0
1	0	Gram-positive coccus	0	0	0 *
0	0	0	1	0	Gram-positive coccus
0	0	0	0	0	0
5	0	Pseudodiphtheroid; 1 gram-positive coccus; 1 mold	0	0	Pseudodiphtheroid; mold
0	0	0	0	0	0
0	0	0	?	0	1 mold; 1 short-chained coccus
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
1	0	Gram-positive coccus	0	0	0

—INFECTIONS IN PATIENTS OVER TWO YEARS OLD

Culture No. 1			Culture No. 2		
Number Organisms per C.e.	Number Gram-Negative Bacteria per C.e.	Types of Organism	Number Organisms per C.e.	Number Gram-Negative Bacteria per C.e.	Types of Organism
1	0	Gram-positive coccus	2	0	Gram-positive coccus
3	0	Gram-positive coccus	2	1	Gram-positive coccus; B. proteus vulgaris
0	0	0	0	0	0
0	0	0	1	1	B. proteus vulgaris
4	0	Gram-positive coccus			
1	0	Gram \pm staphylococcus			
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
1	0	Gram-positive coccus	0	0	0
0	0	0	0	0	0
1	0	Hay bacillus	0	0	0
1	0	Gram-positive coccus	0	0	0

in the first group of cases catheterized. The only case in which there were more than 5 organisms per cubic centimeter was a case in which twenty-one colonies of streptococci grew out of the blood-agar plate. There was no growth on the litmus-lactose plates. The small number of organisms probably all represent bacteria washed in from the urethra. This series of cases consisted of thirteen hospital cases, two acutely ill, the remaining suffering from chronic infections, and eighteen normal children in an orphan asylum.

SUMMARY

In 118 specimens of carefully catheterized urine from sixty-one different girls, sixty-one were sterile and fifty-seven contained bacteria. Of those from normal infants, thirteen were sterile and eleven contained bacteria. Of those from extra-urinary infections in patients under 2 years of age, none were sterile and twenty-four contained organisms. In those from girls over 2 years, thirty-eight were sterile and twenty-two contained bacteria. The number of bacteria found in Series 1 was considerably larger than in Series 2. This may be explained by the fact that in the older children one can cleanse the urethral orifice much easier than in the infant and introduce the catheter directly into the urethra. The bacterial flora was practically the same in both series, gram-positive cocci and diphtheroid organism predominating, the former being present in practically every case in which any organisms were found. In no instance were gram-negative bacilli found in such numbers in both specimens that it seemed probable that it was more than an accidental contamination from the urethra.

CONCLUSIONS

1. Organisms of the colon bacillus group are not normal inhabitants of the female urethra.
2. In extra-urinary infections occurring in the first two years of life the colon group of bacilli are frequently found in the urethra (one-third of the cases).
3. In girls over 2 years of age the urine is almost free of organism, and in our series entirely free from bacilli of the colon group (eighteen normal, twelve other infections).

SYMPOSIUM ON SYPHILIS

FREQUENCY OF HEREDITARY SYPHILIS *

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Reliable statistics on the frequency of a given disease are dependent on two factors: study of large groups of individuals, accuracy of diagnosis. Students of such a problem may compile their statistics from critical analysis of the literature and from their own personal observations. In these personal observations accuracy of diagnosis can be obtained only by careful methods of investigation, both clinical and laboratory; the clinical including an inquiry into the family and personal history of the individual and the practice of making a physical examination; the laboratory including the usual routine tests and, in addition, any methods specially applicable to the subject under discussion.

In accordance with this general plan, we have made an inquiry as to the incidence of hereditary syphilis, drawing our final conclusions from an analysis of the literature and an intensive study on our own part of 695 patients at The Children's Memorial Hospital.

LITERATURE

Comparatively few large groups of cases of hereditary syphilis have been carefully studied by both clinical and laboratory investigations.

Epstein,¹ in a Prague foundling asylum, obtained positive Wassermann reaction in 33 per cent. of 236 newly born infants, and in 10 per cent. of their mothers.

Blackfan, Nicholson and White² found a positive Wassermann reaction in 2 per cent. of 101 hospital infants, that is, in two infants. One of these patients was without symptoms, but gave a complete reaction. The authors accept the specificity of a complete reaction, but consider

* Read before the Section on Diseases of Children at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

1. Davis, E. P.: *Amer. Jour. Obst.*, 1916, lxxiii, 769.

2. Blackfan, Nicholson and White: *AM. JOUR. DIS. CHILD.*, 1913, vi, 162.

the significance of a weak or partial serum reaction as still undetermined (1913).

Holt³ obtained, in 178 hospital children, eleven positive Wassermann reactions, or 6 per cent.

Elliott⁴ (Glasgow) obtained positive Wassermann reaction in 10.8 per cent. of 130 hospital children. He used the method recommended by Browning and Mackenzie, and also adopted the standards of those authors.

Browning⁵ studied 3,000 cases of syphilis as a whole, quoting Watson as follows: Of 331 outpatient department children in Glasgow, forty-six, or 14 per cent., were syphilitic, 10 per cent. clinically and by Wassermann reaction, 4 per cent. clinically only. These patients were carefully studied, especially as to their family history; in all patients with a positive Wassermann reaction some other member of the family also gave a positive reaction.

Jeans and Butler⁶ found in the outpatient department of a St. Louis hospital, among 5,185 new patients, 108 cases (2 per cent.) of hereditary syphilis. But dividing their patients into two groups, those under and those over 13 months of age, the proportion of syphilitics was 4.9 per cent. in the first or younger group, and 1.5 per cent. in the older group. The lower figure in the second group is due to the large number of deaths among syphilitics under 1 year of age. The proportion in the first group, 4.9 per cent., of course represents more correctly the proportion in this particular series.

There is no statement as to the number of Wassermann tests done.

A report⁷ from a children's clinic in Prague states that of 2,533 infants, 5.7 per cent. were syphilitic, either clinically or by the Wassermann test.

Whitney⁸ reports from the outpatient department of a San Francisco Hospital a series of 7,885 patients. There were 915 children, all studied clinically and by the Wassermann test, and 2.9 per cent. were syphilitic.

Of the above eight reports on the incidence of hereditary syphilis, seven are based on both clinical and laboratory (Wassermann) examinations and one apparently on serum tests alone. The four American estimates range from 2 to 6 per cent., the two European (Continental) are 3.3 and 5.7 per cent. The two estimates from Scotland, both from Glasgow, are the highest found, being 10.8 and 14 per cent.

3. Holt: *AM. JOUR. DIS. CHILD.*, 1913, vi, 166.

4. Elliott: *Glasgow Med. Jour.*, 1914, lxxxi, 339.

5. Browning: *Brit. Med. Jour.*, 1914, i, 77.

6. Jeans and Butler: *AM. JOUR. DIS. CHILD.*, 1914, viii, 327.

7. Steinert, E., and Flusser, E.: *Arch. f. Kinderh.*, Nov. 2, 1915, *Abst.*, *Jour. Am. Med. Assn.*, 1916, lxvi, 608.

8. Whitney: *Jour. Am. Med. Assn.*, 1915, lxv, 1986.

One of us (F. S. C.⁹) in 1912 reported a series of 102 infants and children, with thirty-nine positive Wassermann reactions, twenty-nine of which, on the combined basis of physical signs and positive reaction, were regarded as syphilis. In almost all of these cases the reaction was weakly positive, a single plus. In view of recent observations on the significance of an incomplete reaction, further discussion of that paper seems necessary.

During the last two or three years various workers have expressed the opinion that a Wassermann reaction variously described as a "single plus," "incomplete," "faintly" or "weakly" positive, is by no means diagnostic of syphilis, but is found in other conditions. For-dyce in 1914 said that a partial or transient complement fixation is sometimes seen in cachectic states, as well as in leprosy and yaws, and that an indeterminate or weakly positive reaction is of value as an indication for treatment, but of little diagnostic importance unless accompanied by other symptoms.

Nicholas and Gaté,¹⁰ in 1914, working in a dermatologic clinic, report a positive Wassermann reaction in 39 per cent. of seventy-one nonsyphilitic patients, presenting a great variety of conditions, among others impetigo, eczema and pediculosis. They say nothing of the degree of intensity of the reaction in these cases, nor do they give their methods of performing the test. Their results in cases of undoubted syphilis, however, indicate that their technic and methods were reliable. It is possible that in the nonsyphilitic cases their reactions were +, weakly positive. We have ourselves, as described below, obtained such a reaction in cases of eczema.

Craig,¹¹ in 1915, classifies his reactions as ++, +, +—, and —. He interprets ++ as syphilis, regardless of history or clinical signs, and + or +— as always doubtful unless the history and symptoms are well-defined.

Hesse¹² distinguishes two groups of nonsyphilitic disorders in which the Wassermann reaction is positive: (1) protozoa; (2) scarlatina, tuberculosis, malaria, pneumonia, lupus erythematosus, carcinoma and sarcoma. Here, again, we could confirm a weakly positive reaction in certain of these conditions, namely, tuberculosis and pneumonia.

Moore¹³ eliminates a faintly positive reaction without clinical signs and urges a repetition of the test.

It thus becomes evident that too much reliance cannot be placed on an incomplete Wassermann reaction by itself. Either the reaction, if

9. Churchill, F. S.: *AM. JOUR. DIS. CHILD.*, 1912, iii, 363.

10. Nicholas and Gaté: *Bull. Soc. franç. de dermat. et de syph.*, 1914, xxv, 200.

11. Craig: *Am. Jour. Med. Sc.*, 1915, cxlix, 41.

12. Hesse: *Abstract, Am. Jour. Obst.*, May, 1916.

13. Moore: *Jour. Am. Med. Assn.*, 1915, lxx, 1980.

taken by itself, must be strongly positive, or, if weakly positive, must be accompanied by well-defined family history or physical signs, to justify a diagnosis of syphilis. I have, therefore, reviewed my work of five years ago, applying to it our present standard, and find that only five of the original twenty-nine cases will stand the test, and that, therefore, only five of the 102 cases reported in 1912 can be regarded as syphilis, basing the diagnosis now on either a strongly positive Wassermann reaction alone, or on the combination of a weakly positive reaction and well-defined physical signs. This makes the incidence of syphilis in that series about 5 per cent.

THE AUTHORS' PRESENT CASES

We have made an intensive study of 695 cases, unselected, in age from prematurity to 12 years, taken just as they entered the hospital, during the period from Nov. 1, 1915, to June 1, 1916. Of these, twenty-three, or 3.3 per cent., have been found to be cases of syphilis. We have excluded only the children admitted for the removal of tonsils and adenoids. These patients remain in the hospital only twenty-four hours, too short a period for thorough study.

In considering the diagnosis in these cases, due weight has been given to both clinical and laboratory investigations. In addition to the regular routine procedures observed with all cases on admission, special attention has been paid on the clinical side to the family history, to the presence or absence of characteristic physical signs, and on the laboratory side to the Wassermann and luetin tests, Wassermann tests having been performed on every patient, luetin tests on 171 patients. The significance of these various diagnostic methods must be briefly considered.

The clinical history and manifestations may be either suggestive or conclusive. Thus, a history of chancre in the father, of repeated miscarriages or stillbirths in the mother, obtained in the history of an emaciated infant, must be regarded as at least suggestive, even though the infant presents none of the characteristic lesions of syphilis; but if to such a family history be added the observation of one or more characteristic physical signs, such as an enlarged spleen or palpable epitrochlear glands, the diagnosis of syphilis is practically certain; finally, marked characteristic lesions in the infant, such as "snuffles," rhagades, signs about the buttocks or on the palms and soles, can leave no doubt of the nature of the condition, even though we have failed to elicit a specific family history.

The laboratory investigations also may be either suggestive or conclusive. As already stated, two special tests have been applied in this series, the Wassermann and luetin tests.

(A) WASSERMANN TEST

We have considered this test one of the most reliable single signs in diagnosis. In an account of a study of cases which involve the use of this reaction, it should be deemed necessary to give in detail a description of the methods employed in the performance of the tests, together with the values placed on the different varieties of results. Although there has been some tendency toward uniformity and standardization in the technic of the Wassermann test, there are still many variations in the hands of different workers, to some degree necessarily so, as there is still much to be done to improve the reaction. However, in analyzing reports of Wassermann tests, it is important to know not only that results were either positive or negative, but also to know how the tests were made and interpreted. Otherwise, groups of reports from different sources cannot be properly correlated, nor can the correct value always be placed on any particular group of reports. Some aspects of the performance of the Wassermann reaction show no essential variations with different systems; in the case of other points, there are variations, and it has been considered worth while to give the following brief description of the technic employed by us in the present series.

*Technic;*¹⁴ *Hemolytic System.*—Corpuscles: We used washed sheep's corpuscles, 5 per cent. suspension in 0.085 per cent. sodium chlorid solution, 0.5 c.c. being taken.

Amboceptor: The serum of rabbits immunized against the washed sheep's corpuscles was used, 2 titer units being taken.

Complement: Fresh serums of guinea-pigs, undiluted, was used, 0.05 c.c. being taken.

The titers of various amboceptors varied from 0.0003 to 0.00004. Very satisfactory amboceptors from the points of view of both titer and stability were obtained by the method recommended by Coca.¹⁵ The amboceptor was always titrated before performing the tests.

Antigens: The type of antigen used in all the tests was the acetone-insoluble variety, consisting of a saline suspension of a methyl alcohol and ether solution of the acetone-insoluble fraction of an ethereal extract of the residue after evaporation of an alcoholic extract of minced beef heart. This type of antigen was used in twice the amount, giving complete inhibition of hemolysis with syphilitic serums, this amount being one-tenth, or less, of the amount giving anticomplementary action by itself. With alcoholic extracts of guinea-pig hearts, used in some of the cases, as satisfactory results were usually, though not always, obtained.

14. The technic is similar to that in use at the laboratory of the Boston City Hospital.

15. Coca: Jour. Infect. Dis., 1915, xvii, 2.

Cholesterin antigen, 0.4 per cent. cholesterin (Kahlbaum) in absolute alcohol, was used in over 200 of the tests, but the results with this antigen are of more value in following antisyphilitic treatment than in aiding the diagnosis. Of 220 cases in which the tests were made with this antigen and with the acetone-insoluble variety, there were 202 in which there was close accord in the results; of the remaining eighteen tests, thirteen showed partial fixation with the cholesterin, and none with the other antigen, and five gave almost complete hemolysis with the latter and complete with cholesterin.

Our experience with cholesterinized antigens tends to confirm the conclusions drawn by other workers with these antigens, that cholesterin added to alcoholic extracts makes them more sensitive as antigens in the Wassermann reaction, but less specific. Recent work by McClure and Lott¹⁵ makes for confirmation of this opinion.

For use in the tests the patient's serum was inactivated at 55 C. in a water bath for thirty minutes. The method of performing the tests was to place 0.1 c.c. of the inactivated serum from each patient in separate tubes (100 by 12 mm.). To each tube there was then added complement, amboceptor, and antigen, in the amounts above indicated, the bulk of liquid in the tube then being made up with saline solution to 1.1 c.c. The tubes were then incubated at 37.5 C. in a water bath for thirty-five minutes, when the corpuscle suspension was added to each tube and the tubes returned to the water bath for one hour. Controls with known negative and positive serums were run simultaneously. Tests showing any degree of inhibition of hemolysis were repeated without antigen to check anticomplementary action of these serums.

Results and Interpretation.—Positive reactions have been grouped in three classes. Those in which there was complete inhibition of hemolysis have been designated as + + +; those showing a considerable degree of inhibition, but distinct hemolysis above the unhemolyzed corpuscles, as + +; and, lastly, those with hemolysis almost complete, but with undissolved corpuscles in small amount still remaining, as +. A + result alone has almost no value in diagnosis; it sometimes is of help when occurring in the course of treatment after a + + + result. The + + result with distinctly suspicious clinical signs may clinch the diagnosis of syphilis. The + + + reaction gives a positive diagnosis, but in the absence of any suspicion clinically, a repetition of the + + + reaction should be obtained. When the clinical picture is entirely negative and the Wassermann test is + or + +, a repetition on the blood collected later will frequently be negative; conditions other than syphilis, which may sometimes give partial inhibition of hemolysis in the test, are a few acute

16. McClure and Lott: Am. Jour. Med. Sc., 1916, cii, 5.

infections, during the period of elevated temperature especially, and certain chronic affections, such as tuberculosis. These transitory nonsyphilitic + and ++ reactions are infrequent. It may be of interest to note that of fourteen cases of eczema in the present series, without any suggestion of syphilis, four gave a + or ++ Wassermann. Conditions giving false positives or false negatives in the adult are not considered here.

(B) LUETIN TEST

We have applied the luetin test in 170 cases, nine syphilitic, 161 nonsyphilitic. Among the syphilitic cases there was one positive (pus-tular) reaction, one suspicious (papular), and seven negative results. Among the nonsyphilitics there were four positive reactions (one pus-tular and three papular), eight suspicious, and 149 negative. Thus, this particular test was of little diagnostic value in our series. The material used was direct from Noguchi's laboratory, and his written directions were carefully followed. Our cases are too few in number, however, to warrant any conclusions as to the diagnostic significance of the test.

ANALYSIS OF CASES

Our whole series of 695 cases, studied according to these methods, has been divided into the syphilitic and the nonsyphilitic classes, brief and condensed analyses of which are here given.

Cases Considered Syphilis.—We have accepted twenty-three cases as undoubtedly syphilitic. They may be grouped as follows:

Group 1, cases with distinct clinical signs, but negative Wassermann reaction, one case.

Group 2, cases without clinical signs, except poor nutrition and general adenopathy, but with Wassermann reaction + + +, six cases.¹⁷

Group 3, cases with both clinical signs and positive Wassermann reaction + + + in fifteen cases, + + in one case, sixteen cases.¹⁸

Thus, six of the twenty-three cases had no clinical manifestations of the disease, and a diagnosis is impossible except by the presence of a complete or + + + serum reaction.

Seven of the twenty-three patients died. Necropsies obtained on three of these showed syphilitic changes in all of them.

Cases Not Considered Syphilis.—The cases considered as nonsyphilitic number 672, and group themselves in more or less definite classes. In the first class there is nothing suggestive clinically and the Wassermann reaction is negative. They number 640. In most of these cases

17. Diagnosis was confirmed by necropsy in one case.

18. Two diagnoses were confirmed by necropsy. Spirochetes were found in the liver.

the test was done on the blood once only, in six on the blood twice, in sixteen on both the blood and spinal fluid, in one on the spinal fluid alone.

Doubtful Cases.—Three children with a single negative Wassermann and two with two negatives, all clinically suspicious, have been grouped in this class:

Maurice R. had a family history which was suggestive, but otherwise negative. One Wassermann test was made, which was negative.

Mike M. showed epitrochlear nodes and an enlarged spleen as the only signs. One Wassermann was made, which was negative.

Caroline R. had three miscarriages. A luetin test was positive, which was only suggestive, and one Wassermann test was made, which proved negative.

Mildred H. showed keratitis and adenopathy. Two Wassermann tests were negative and one luetin test was positive.

William K. showed suspicious teeth and general adenopathy, including enlarged epitrochlears. Two Wassermann tests were made, both of which were negative.

For statistical purposes, these children cannot be regarded as syphilitic, yet for their own future development, they should be watched, and repeated serum tests should be done.

Another class comprises seventeen cases with no clinical signs, but with an initial + or ++ Wassermann and a subsequent negative reaction. Included in this class, however, are two exceptions, slightly suspicious clinically: Verna H., nose slightly flat, Wassermann ++, later negative; Victoria O., six weeks old, eruption on face and buttocks for two days, Wassermann +, later negative.

There is still another group of fourteen cases in which only one test of the blood was made, giving either a + or ++ reaction. None of these patients had the slightest suspicion of syphilis clinically. Consequently, in view of our interpretation of an incomplete reaction, we cannot accept them as cases of syphilis.

One more nonsyphilitic case needs special mention. It showed no clinical evidence of syphilis; the Wassermann on the blood was negative, but ++ on the spinal fluid. The case was one of tuberculous meningitis.

Serum tests have been done on the mothers of sixteen nonsyphilitic children, which proved to be + in one, negative in fifteen.

CONCLUSIONS

Statistics as to frequency of any given disease must be based on large numbers of patients, carefully and accurately studied as to diagnosis.

The diagnosis must be made after judicious weighing of all the evidence, both clinical and laboratory.

Study of the literature on the incidence of hereditary syphilis shows a wide range of results, it being variously estimated at from 2 to 14 per cent., in Europe and America.

Intensive study of a group of 695 patients in The Children's Memorial Hospital, during the winter of 1915-1916, the study embracing both clinical and laboratory methods of investigation, shows an incidence of 3.3 per cent. of hereditary syphilis.

The amount of hereditary syphilis among the hospital infants and children in four large cities of the United States, New York, St. Louis, San Francisco and Chicago, appears to range from 2 to 6 per cent.

We are indebted to Dr. Noguchi for the luetin used. Our thanks are also due to Dr. A. B. Schwarz, Resident Physician, for much valuable help in the prosecution of this work.

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CLINICAL COURSE AND PHYSICAL SIGNS IN HEREDITARY SYPHILIS OF EARLY AGE *

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Even a casual reading of modern textbooks shows a marked and irreconcilable variation in the descriptions of infantile syphilis. It seems wiser, therefore, to write only of such portions of the subject as have come within personal experience, rather than to attempt a finished treatise, which must, of necessity, include quotations or adaptations from others. This paper will therefore contain few quotations and few conjectures or theories, and will show very serious omissions, if one expects an exhaustive treatment of the subject.

The terms applied to syphilis of the infant need definition: "Infantile syphilis" includes hereditary, congenital and early-acquired syphilis. "Hereditary syphilis," strictly used, refers only to those cases in which the parents, one or both, were syphilitic at the time of conception. "Congenital syphilis" refers to those cases in which the mother is infected during pregnancy.

The last two terms are often used interchangeably, and the distinction between the children included under the different terms is little known, but there should be a distinction made between a fetus syphilitic *ab initio* and one rendered syphilitic after a healthy start. Studies in this direction have not been sufficient to allow accurate distinction, but it will probably develop that the congenital defects, the dystrophies, so common in syphilitic babies, are practically confined to hereditary cases. The term "hereditary syphilis" is often contracted to "heredod-syphilis."

The relation between parents and offspring has been, and still is, the subject of grave discussion. Clinical observation allows a few statements, without any attempt at theory, which, it seems, might be universally accepted. Syphilitic children are born when the father is syphilitic, when the mother is syphilitic, and of course, when both parents are syphilitic. A pregnant woman who becomes syphilitic transmits the disease to her fetus. A baby born syphilitic may suckle its apparently healthy mother with impunity. A syphilitic mother may suckle her apparently healthy baby, born while she was syphilitic, with impunity.

* Read before the Section on Diseases of Children at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

There may be exceptions to these rules, but not sufficient in number to invalidate their general truth.

Hereditary syphilis occurs in a great variety of clinical forms, differing according to the disease of the parents and carrying out the original protean character of the disease. The disease may affect the whole organism, or be manifest only in a single organ. The variety is therefore infinite. The baby may show the severest form or present such an appearance of health that one is with difficulty convinced that it is in any respect syphilitic. The clinical course of these various forms is somewhat different. One class of children who show severe disease at birth, and might well be described as having early malignant syphilis, merits a special and separate description.

These children are usually premature. They are emaciated; they snuffle and cry hoarsely. An eruption is soon apparent of bullae, situated chiefly on palms, soles, wrists and ankles. These bullae are flaccid and partially filled with seropurulent fluid. Some of these burst and leave red, angry-looking spots deprived of their epidermis. The lips are cracked and ulcerated; crusts form at the nostrils. The liver and spleen are enlarged and digestion is evidently very imperfect.

These children purse with difficulty because of the condition of the nose. They cry all night, as if in pain, and in the daytime when handled. They become extremely emaciated and usually die within a few days or weeks of their birth.

These extreme cases form only a small portion of the total number of cases of heredosyphilis, but they are striking. They are easily recognized; they have often been described and figured and form the ideal syphilitic baby for both lay and professional opinion. Their extreme emaciation has led to the use of the term *marasmus* as practically synonymous with syphilis. The extreme or malignant cases of acquired syphilis have been used in the same way as examples of the disease.

From these emaciated and feeble specimens all gradations appear, up to babies whose condition cannot clinically be distinguished from health. But soon these apparently healthy children, for the most part, show something which justifies at least a suspicion of a syphilitic heredity. The study of the younger children of a syphilitic family, those in whom the disease is poorly marked and late in showing itself, is the best possible preparation for the recognition of syphilis in doubtful cases. Evidence of intra-uterine disease is often revealed by careful study of the babies brought living into the world.

WAKEFULNESS

One of the early symptoms which ought to attract attention is obstinate wakefulness. The child cries almost unceasingly at night and cannot be pacified. During the day he is quiet, so long as he is unmolested, and sleeps; but every night there is the same unceasing cry.

In many of these cases the baby's cries are only increased by handling, and the cry indicates pain.

Many of these cases of wakefulness are due to disease of the bones and their characteristic nocturnal pains similar to those affecting adults with acquired syphilis. The matter will be further discussed under the head of bone syphilis.

SNUFFLES

Nasal catarrh attacks a very large proportion of syphilitic infants, and gives rise to a most characteristic symptom. It appears early, often, if not always, preceding the eruption. It shows itself at the beginning by difficult and noisy respiration. The mucous membrane of the nose becomes swollen, and partially closes the nasal passages. A nasal discharge appears and increases, still further occluding the passage, and acts as a valve with each respiration, which becomes noisy. The symptom thus caused is known as snuffles. The discharge from the nostril is seropurulent in character at first and often streaked with blood. In severe cases this discharge runs down over the upper lip, which becomes reddened and excoriated. The difficulty of respiration increases; the discharge becomes purulent and dries into crusts, which may entirely close the nostrils and oblige the child to breathe through the mouth. In such cases nursing becomes difficult and often impossible; the child, obliged to relinquish the breast every moment to get breath, is fed very imperfectly, and sometimes weans himself.

The nasal symptoms may be very persistent, being the first to appear, and continuing months after other symptoms have vanished. In some cases the snuffling is not very noticeable so long as the child lies quiet and breathes through the mouth, but the difficulty becomes at once apparent if he is disturbed, and even more marked when he takes the breast.

Marshall quotes from Gastou a discussion of rhinitis in several forms which is quite striking and well worthy of quotation:

Gastou describes the following forms: (1) Anterior rhinitis, which only differs from simple coryza by its long duration and the occurrence of fissures and erosions about the nose. This form is generally benign. (2) Posterior rhinitis, which is accompanied by slight discharge, but causes troubles of respiration and deglutition. This form is readily curable by mercury. (3) Subacute adenoiditis, which is rarer than the above, and generally follows them. It begins with acute pharyngitis, and continues with symptoms of adenoid vegetations. It is often complicated by otitis, laryngitis, and bronchopneumonia. It is cured with difficulty, and always leaves an inflammatory residue, which later on develops into adenoids. (4) Suffocating rhinolaryngitis, which is sometimes fatal soon after birth. The mucous membrane is dry and swollen, and its sensitiveness causes spasm of the glottis and sudden death. (5) Septic rhinopharyngitis, which is usually a complication of the other forms. This may be the origin of infectious lesions affecting other organs. In the acute form there is a fetid seropurulent discharge; in the subacute form, laryngeal and pulmonary complications, which are often fatal; in the chronic form, signs of septicemia, with visceral lesions and cutaneous ulcerations.

ADENOIDS

Few children with the snuffles of hereditary syphilis escape a diagnosis of adenoids and an operation. The symptoms are the same, whether the breathing is obstructed by adenoids or by narrowed nasal passages, such as occur in heredosyphilis. In syphilis relief is seldom obtained by operation, and we find the operation repeated and sometimes a third operation being done.

The upper jaw is known to lack proper development, so that the upper incisors fail to meet the lower, as was pointed out by Dr. Hutchinson in his observations on the deformity of the upper central incisors known by his name. The very high arched palate is another example of a deformity in the same bones; and Roentgen-ray studies of the facial bones show that the nasal passages are decidedly narrowed, so that the symptoms attributed to adenoids are really due to congenitally narrow nasal passages occluded by the swollen mucous membrane.

The objection to operations on syphilitic snuffles for adenoids is not alone that it is generally useless, but also that it exposes the physician to risk of inoculation. I have had the unpleasant duty of treating one enthusiastic operator for chancre of the finger. I have been told of another case, and even two cases are enough to warrant hesitation in doing an ill-advised and gratuitous operation.

CRY

Syphilitic babies, especially those in whom the snuffles is marked, have also a peculiar cry. It is at once hoarse and high pitched. It may not be diagnostic, but its character is such as to indicate that the same condition which causes the snuffles involves also the region of the vocal chords. Like the disease of the nose, the pathologic condition varies from simple inflammation and swelling of the mucosa to actual ulceration of mucous membrane and destruction of soft parts and cartilage.

MARASMUS

The marasmus of syphilis sometimes appears in infants who show in themselves little other evidence of the disease, and continues until the baby is reduced to the condition of a living skeleton. In breast-fed or carefully nourished infants who continue to waste without evidence of other disease to explain the phenomenon, a suspicion of syphilis should always be aroused, and a diagnosis may sometimes be made from the family history.

The term marasmus has become a synonym for hereditary syphilis in death certificates, for few deaths from hereditary syphilis are reported as such. Marasmus has very properly been dropped from most nosologies, but instead of forcing the certifying doctor to make a proper return, so far, it seems to result in still wider falsification of death returns.

LOSS OF WEIGHT

The healthy infant loses weight for a few days, but soon regains the loss and continues to gain. The syphilitic infant gains much more slowly, even in spite of the utmost care in feeding.

There is, in the Syphilitic Department of the Massachusetts General Hospital, under the care of Dr. Morton Smith, a baby, K., admitted on February 28 at the age of 3 months. Its mother has a positive Wassermann; the whereabouts of its father is unknown.

The baby was premature, was breast fed for one week, then had two breast feedings per day. On its seventh day it was admitted to the eye and ear infirmary with ophthalmia (character not reported), and remained there for six weeks. It had an eruption on the buttocks at 6 weeks, which became universal. Since discharge from the Eye and Ear Infirmary it has failed to gain weight. It is poorly developed, almost marasmic. It has fissures about the anus, definite temporal baldness, and hair thin generally. It has general glandular enlargement, occipital, submental and inguinal. Its nasal bones are rudimentary and it has slight snuffles. The liver is 2.5 cm. below the costal margin, and the spleen is just palpable. A soft systolic murmur is perceptible at the apex. It had marked fat intolerance during its stay in the hospital. Paracentesis of both ear drums has been necessary.

It has been most carefully tended and its feeding superintended by doctors from the children's department; but in spite of every care it has gained with wonderful slowness.

ADENOPATHY

Syphilis shows a marked tendency to involve the lymphatic system. The systematic examination of lymphatic nodes is part of the routine examination for suspected syphilis in the adult. The glandular system is of equal importance in the hereditary cases, though the opposite has usually been taught. The lymphatic nodes have the same characteristics as in the acquired disease; that is, they are multiple, noninflammatory, not painful, perfectly distinct and movable. Only occasionally do they suppurate except in the neck, where they are regarded by many clinicians as evidence of tuberculosis. The peribronchial glands and those of the omentum and mesentery have been found enlarged in post-mortem examinations. The peribronchial glands occasionally play an important part in the clinical history of the affected child.

SKIN

On those cachectic subjects in whom emaciation is marked the skin hangs in folds, but such wasting is little noticeable in the less seriously affected babies. In many subjects the skin has a pale, sallow, earthy, sometimes yellowish hue which is regarded by some writers as

characteristic. Wegner, in his article on osteochondritis, suggested that the anemia and pallor might be due to disease of the bone marrow. In a few cases under observation, extreme pallor and marked bony changes have coincided. The change in the spleen must also be suspected.

The skin lesions of hereditary syphilis are marked by a tendency to become confluent and form large plaques, and also to desquamation and ulceration. Perhaps the multiform character of syphilitic dermatoses is more marked in infantile hereditary disease than in the adult acquired.

The most common eruption of heredosyphilis is the maculopapular, sometimes one element predominating, sometimes the other. Often the first evidence on the skin is the redness of the soles. This redness usually shows first on the heels, where it is darker colored than the rest of the sole and actually shines. Desquamation is common, often in flakes, which are very large in proportion to the size of the foot. Distinct papules are sometimes evident in the midst of the general redness. The palms show the same characteristics, though desquamation is even more common in the palms than in the soles.

The maculopapular eruption is usually first seen under the diaper in discrete lesions of perhaps half an inch in diameter. It may be confined to this region, but may extend over the whole body, varying very much in the total number of lesions. The color is the same dusky red, so difficult to describe in adult disease; the difficulty lying very largely in the fact that no one term can describe its varying appearances. Ulceration of separate papules is very common in the warm, moist region beneath the diaper.

Cracks and ulcerations about the lips, especially the corners of the mouth, are common. These ulcerations are transverse to the borders of the lips and radiate from the corners of the mouth. Such cracks and fissures occur with varying severity. Similar fissures radiate from the anus. The scars left by these fissures are of great value in diagnosis in later childhood and early adult life. They are referred to ulcerations of infancy. Some observations of late seem to justify the belief that these cicatrices are occasionally due to intrauterine disease. When I have made the remark that certain children must have had very sore mouths in infancy, the mothers have disputed my statement, and careful examination has occasionally shown cicatrices already existing, even in early infancy. A case in point shows a baby's face with abundant active ulcerations of the lips. About the mouth and on the cheeks are marks probably of ulcerations which were prenatal, possibly failures in development, similar to such defects as the failure of development of the nails, an example of which Dr. Wile published not very long ago.

Confluent Macula.—The macular eruptions often coalesce into large plaques on the face, about the genitals, and in the folds of the neck.

They may form such a plaque about the nose and mouth, extending on the forehead and chin, with an outline which hints at an original formation from circular spots which have united and with smaller distinct and separate circular spots in the neighborhood. The plaques are reddish or coppery in color, slightly raised. They desquamate rather freely. One unfamiliar with them might mistake them for eczematous patches, but they are quite distinctive and their distribution is diagnostic.

Such a plaque, covering the vertical middle third of the face, spreading over the eyebrows above and including the nostrils, closed by crusts, with lips cracked, ulcerated and bleeding, makes a characteristic picture.

Annular lesions occur with the same frequency as in acquired disease and in greater numbers on a single individual. One baby showed several circles on the neck, the wrists and one buttock and thigh were practically covered. They intersected and showed entire circles and segments of circles. They had been regarded as ringworms, according to the mother. One patient showed a series of rings arranged about the anus, which had ulcerated under the influence of heat and moisture. Another showed a series of intersecting rings on one buttock, so delicate that they could only be seen in certain lights.

Boils, Abscesses.—Occasionally a series of "boils" appear on a syphilitic baby. These are distributed widely over the body, six, eight or ten in number. They have a diameter of one-half or three-fourths inch. They open by a little hole in the center. In fact, they behave like gummas of the skin, which undoubtedly they are. Those cases in which they occur are usually severe. They may occur alone or as part of a general eruption.

More distinct abscesses occur occasionally and seem of a different nature.

Bullous eruptions occur at a very early age. They are either present at birth or appear very shortly after. The lesions occur about the hands and feet, though they are not necessarily confined to these localities. The bullae vary from one quarter to three quarters of an inch in diameter. They are flaccid, only partially filled with turbid fluid, which is sometimes mixed with blood. They are easily ruptured and the loosened epidermis partially covers the reddish base. They indicate a serious form of disease, which usually, but not always, ends fatally. Other forms of eruption may be present at the same time.

ONYCHIA

Onychia of the nails is quite common in syphilitic infants, but it varies in character. All the nails may be affected, or more commonly only a minority, perhaps only one. Usually there is thickening, dis-

coloration and gradual separation of the nail from its bed. It may be a noninflammatory process, attracting no attention and only seen if looked for. On the other hand, there may be inflammation and supuration, with all the pain and tenderness that attends onychia in the adult, and paronychia. In both forms the nail may be shed repeatedly before a permanent nail is produced.

ALOPECIA

Loss of hair is one of the important characteristics of heredosyphilis. It is found at birth in a large proportion of cases, being one of the evidences of intrauterine disease. It occurs in various forms, but seldom, if ever, as a complete loss. It is usually a general thinning of the hair. Sometimes it shows chiefly as an exaggeration of the natural bays over the temples. The loss of eyebrows at the same time may be taken to mean syphilis. The remaining hair often presents a dry and unhealthy appearance.

CRANIAL EXOSTOSES

Cranial exostoses of syphilitic infants were described by Parrot, who regarded them as incontestible proof of syphilis. They are flattened elevations of variable prominence and extent, of a circular contour, sometimes elongated in one or two directions. They have four seats of predilection, the two frontals and the two parietals. Ordinarily they are symmetrically placed in regard to the frontal and sagittal sutures, but not always. These cranial exostoses are by some attributed to rachitis, but they occur long before the age at which rickets occurs and in conjunction with very evident syphilis.

Disease of the bones is one of the most important of syphilitic manifestations. It begins before birth and during infancy furnishes evidence of intrauterine disease; it is a cause of some of the most distressing of infantile maladies, and plays a very important part in differential diagnosis. It needs careful study because of the danger of mistaking it for rickets, scurvy, tuberculosis or some of the rarer forms of bone disease. Hereditary bone syphilis may present all the forms of the acquired disease occurring in bones that have reached their growth. In addition to these it has certain forms of its own, as it occurs in bones in their formative period.

Perhaps the most important of the manifestations of syphilis in the infant skeleton is the retarded ossification at the line of growth known as osteochondritis. This pathological change was described by Wegner, assistant in Virchow's clinic in 1870, though other observers have contributed to our still imperfect knowledge. This change is confined to the long bones. It is not found in all syphilitic infants, or in all the bones of any one baby. There is also present at the same time perios-

titis, sometimes involving seriously a number of bones. These changes require serious anatomical research. They have been studied by frozen sections, but radiologic pictures disclose the condition of the whole skeleton at one time and during life.

As shown in the Roentgen-ray picture, the line of demarkation between diaphysis and epiphysis is broader and in the extreme development of the disease there is shown a displacement of the epiphysis. There is almost always marked periostitis of some bones. When one looks on the radiologic picture, it is very easy to understand why the baby cries when he is moved and why he cries so unceasingly. The subluxation of the epiphysis may be recognized in the radiograph. It is the cause of the pseudoparalysis known as Parrot's.

BABIES BORN AFTER THE ADMINISTRATION OF SALVARSAN TO THE MOTHER

It is pretty evident that salvarsan administered during pregnancy to mothers who have previously borne syphilitic children brings about a great improvement in the succeeding baby, but does not always entirely remove the syphilitic taint. These babies are plump and apparently healthy, but with square heads and scanty hair or other suspicious condition. One of them had a very marked alopecia; one had a few flat papules about the face, which were considered to be syphilitic. This child had several abscesses, one of which communicated with the elbow, which healed with a stiff joint.

Of course the condition of the family in regard to syphilis will have much to do with the result. In one case of such a baby as is described above, the pregnant woman received an inoculation of syphilis in the tonsil quite early in her pregnancy. The syphilis was allowed to gain considerable headway before it was recognized. She had had an extremely well-marked secondary eruption for some weeks before she received any treatment. She then received salvarsan and mercury. The child was the child of parents healthy at the time of conception and it is impossible to know just how much credit should be given the salvarsan.

Babies of parents treated by mercurials resemble those whose parents were treated by salvarsan. Whether it is possible to draw a distinction between the two classes of babies remains undecided, but the babies seen after the administration of salvarsan are especially noticeable.

TWINS

It often has been asserted that one twin may be severely affected while the other escapes entirely. There are at present two pairs of twins in attendance at the Massachusetts General Hospital outpatient department. Of the first pair, one has well-marked snuffles, marked

pallor, shining soles and maculopapular syphilis, confined to the region of the diaper and inclined to ulcerate, and marked glands in the groin. It is practically unable to move the left arm, though it moves its fingers. It cries when either of its arms or legs is moved, but has not entirely lost the power of movement. All the bones of the extremities seem to be tender to touch. The second baby, a girl, when seen had a much better appearance, was fatter and had better color, but had a confluent macular eruption specially marked on the right buttock.

In the second pair of twins the children are about equally affected, and are both markedly syphilitic.

Van der Bogert¹ reports twins, one mongolian, with positive Wassermann, the other normal, with negative Wassermann.

DIAGNOSIS

The diagnosis of hereditary syphilis in the infant may be the simplest possible in the severe cases in which the wasting and external manifestations are prominent, or it may present one of the most difficult problems in medicine.

The syphilographer is occasionally asked for an opinion in regard to a very young baby which presents no certain signs. It is often necessary to formulate his opinion on a series of symptoms, no one of which is sufficiently marked, by itself alone, to permit a certain diagnosis. He should listen for noisy breathing, not evident when the baby is sleeping, and listen to its cry. The hair should be carefully observed and the veins of the scalp. The soles need special inspection. The characteristic redness appears first on the heels. It is often marked on the heels when it is not noticeable on the palms. Occasionally, it is the first and only sign present for a time. Careful radiologic study is going to be a great aid in diagnosis.

Fournier² says:

Given a patient upon whom we suspect a hereditary syphilis, never fail to examine the skeleton, bone by bone, without allowing ourselves to be deterred from that examination by the absence of a history of an anterior bony lesion, or even by the denial of such lesions. Since it is possible that from such an examination will come the demonstration of an unknown bony lesion, ignored or even forgotten, and it is unnecessary to say how great will be the interest of such a discovery.

The advantage of such an examination has been greatly increased since the advent of the Roentgen ray, which confirms the testimony of our fingers and reveals a still greater number of lesions which escape the most careful manual investigation, and although that advice was given in regard to children of more advanced years, it has its application to infancy.

1. Van der Bogert: *AM. JOUR. DIS. CHILD.*, 1916, xi, 55.

2. Fournier: *La syphilis héréditaire tardive*, 1886, p. 274.

CLINICAL SIGNS AND DIAGNOSIS OF LATE HEREDITARY SYPHILIS *

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RELATION OF LATE TO EARLY SYPHILIS

The division between early and late hereditary syphilis is largely arbitrary, but, in general, the term "late" is applied to those manifestations which are analogous to the tertiary and quaternary symptoms of acquired syphilis. Having the division on such a basis causes the two types to overlap considerably in regard to age. We may have late lesions as early as birth and early lesions as late as 5 or 6 years of age. As to the upper age limit at which manifestations may occur, none has been established. Changes peculiar to hereditary syphilis are found regularly in the third decade and there are some, notably Fournier, who claim to find manifestations with considerable frequency up to the seventh decade.

The clinical cause of the development of the late type of lesion, as well as the longer or shorter interval between the manifestations of invasion and the late lesions, has remained largely unexplained. The most reasonable explanation is that offered by the hypothesis of Henry Head,¹ according to which there develops a sensitization on the part of whatever body cells come in contact with the spirochete during the invasion or early period. The fuse of the tertiary lesion is then touched off by the appearance in the neighborhood of these sensitized cells of a few spirochetes, which make their appearance from whatever viscus or part in which they have been quietly reposing. Such a course of events seems highly probable and is the only explanation up to the present time which harmonizes with the facts. The division into early and late, in the light of this hypothesis, is relegated to its proper place. It is not a matter of when these organisms start on their journey, but where they go.

During the latent stage, previous to the onset of the late lesion, there may be no stigmata whatever, the child may be above the average in mental and physical development and the only evidence of a persist-

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* From the Department of Pediatrics, Washington University Medical School, St. Louis.

1. McIntosh, Fildes, Head and Fearnside: *Brain*, 1913, xxxvi, 1. Fildes and McIntosh: *Brain*, 1913, xxxvi, 193. Head and Fearnside: *Brain*, 1914, xxxvii, 1. McIntosh and Fildes: *Brain*, 1914, xxxvii, 141.

ing infection may be a positive Wassermann reaction. There is but little literature on these latent cases, which at any time quite unexpectedly develop an active lesion. The question has arisen whether or not in such cases the patient should be treated. Since the Wassermann reaction is an expression of activity on the part of the spirochetes, it has seemed advisable to carry out the treatment just as if an active manifestation were present. The interesting occurrence in our patients so treated has been the frequent onset of an interstitial keratitis shortly after beginning an intensive treatment, comparable to the aggravation under intensive treatment of an interstitial keratitis that had already begun. This latter has occurred in a large number of our cases. In spite of this unpleasant complication, we still believe that in a latent case a patient should be treated. The very fact that this complication occurs is proof of a potential lesion not yet manifest and it is probable that it would become manifest later without treatment.

NERVOUS SYSTEM MANIFESTATIONS

The contributions of Head¹ and his co-workers are probably the most important on the subject of syphilis in the recent literature, and though dealing exclusively with nervous manifestations of acquired syphilis, the ideas are equally applicable to the hereditary infection. The acceptance of their views will increase our ability to classify and study syphilis of the nervous system and avoid much confusion that now exists. They divide syphilis into two main types, syphilis meningovascularis and syphilis centralis, both of which are usually preceded by early symptoms, which they enumerate as follows: Changes in character, behavior, aptitude and memory; disturbances of balance between emotion and reason, headache, changes in sensibility, all forms of disturbance of sleep, nocturnal psychoses, neurasthenic symptoms, attacks of shivering and fever and neuralgic pains due to root lesions. Syphilis meningovascularis includes all the subacute, chronic, tertiary and gummatous lesions, all having the same essential pathology, whether secondary or tertiary. Syphilis centralis includes all the so-called parasyphilitic affections. These have been considered by the majority of writers as purely degenerative processes, primarily, and vascular and glial proliferations, secondarily. Head holds that this lesion has essentially the same pathology as all other nervous lesions and is a reaction, not a degeneration. He holds that both the tertiary form and parasyphilis are due to hyperallergie, as already mentioned. The difference in the anatomic consequences depends on the nature of the tissues involved, which is blood vessels and their connective tissue in one case and highly specialized structures in the other. In the central variety the resulting clinical manifestations depend on the route and the destination of the invading spirochetes, which is along the

posterior columns and roots in the case of tabes and in certain cerebral convolutions in the case of paresis. All varieties of borderline cases between tabes and paresis as well as manifestations which fit into neither group are to be expected. The meningovascular variety is amenable to treatment, but the lack of benefit observed in the central type is due to the fact that nerve cells are already dead and even more to the fact that our present remedies can not reach the spirochetes. Often there is no active lesion to treat, for "instead of a flame we have dead ashes." The Wassermann reaction as standardized and determined by them and its behavior under treatment is used to a large extent in the differentiation between the central and meningovascular types.

Contrary to what is apparently the general impression, lesions of the nervous system in hereditary syphilis are quite common, occurring in nearly 50 per cent. of our late cases. Of the clinical diagnoses, cerebrospinal syphilis comprises much the largest group. This is due to the fact that syphilis of the nervous system assumes such infinite varieties that it is useless to attempt to separate manifestations into types. For clinical purposes cases may be grouped roughly according to the situation chiefly affected. The common pathologic lesion is a meningo-encephalitis or myelitis, either associated with or caused by an endarteritis. Certain syndromes, because of their interesting features or of their frequency, will be briefly discussed.

Chorea.—Several authors² have recently interpreted their observations as showing the absence of relation between choreic symptoms and syphilis. We have observed a number of patients in whom both diseases existed and in but one was there any relation between the syphilis and the choreic symptoms. In that one case³ the fact that the symptoms were due to syphilis seemed established by the therapeutic test. A maniacal chorea was converted into a mild case in twenty-four hours by a dose of neosalvarsan and was completely cured in the course of a few days by the same therapy.

Epilepsy.—Epileptiform seizures differing in no demonstrable way from idiopathic epilepsy may be the direct result of a syphilitic infection. Of our own cases of epilepsy about 20 per cent. were so caused. From the point of view of prognosis it would seem clearer to consider this manifestation in Head's scheme of classification since both types occur.

Multiple sclerosis probably does not occur in childhood, but not infrequently we find patients presenting symptoms quite similar to those of this disease. One such case, which was apparently due to

2. Comby: Arch. de méd. d. enfants, 1915, xviii, 517. Koplik: Arch. Pediat., 1915, xxxii, 561.

3. Veeder and Jeans: AM. JOUR. DIS. CHILD., 1914, viii, 283.

syphilis and which responded fairly well to syphilitic treatment, has come under my observation. The pathology of multiple sclerosis is essentially different from that of a case presenting similar symptoms due to syphilis. The latter symptoms are caused by multiple foci of encephalomyelitis, while multiple sclerosis is a myelin sheath degeneration, noninflammatory in character, vessels not being involved, with no secondary degeneration and the axis cylinder remaining intact.

Hemiplegia, in our own material at least, is the most frequent variety of acquired paralysis due to syphilis. Of twelve cases of hemiplegia, six apparently had a syphilitic basis. Savy⁴ reports seven necropsies and Pehu and Gardere⁵ one on this type of case and the findings in all were practically the same, an encephalitis associated with a syphilitic arteritis. These authors emphasize the fact that the pathologic picture anatomically and histologically differed in no way from other forms of encephalitis and conclude that it is necessary to place syphilis among the infections capable of producing acute encephalitis and give it an important place in the etiology. Acquired paraplegia and diplegia may also occur as a result of syphilis. Paraplegia occurring as a manifestation of late syphilis is often of the spinal or flaccid type, though cerebral symptoms are usually associated. The onset may be sudden or gradual, with pain and sensory disturbances. Such symptoms may be caused by a circumscribed myelitis or gumma, or by a diffuse myelitis over a whole cross-section of the cord. An endarteritis is usually the cause of the myelitis or at least is associated with it.

Mental deficiency of varying grades is a very common finding as a result of syphilis. When occurring as a manifestation of late syphilis, it is more often found associated with other symptoms, such as fixed pupils, paralysis or a complicated brain syphilis. Taking all cases of mental deficiency, we find the number due to syphilis is relatively small, but among the late syphilitics more than one third in our material show this disorder.

Brain tumor symptoms caused by syphilis are relatively rare. When present, they are usually caused by either a gumma, encephalomalacia, or a circumscribed meningovascular process.

Parasyphilis, meaning syphilis centralis in the terminology of Head, is a rather frequent finding in children, but in its usual sense, meaning optic atrophy, tabes and paresis, it is uncommon. We have observed one case of primary optic atrophy in a patient as young as 4½ years. Tabes is seldom diagnosed in children, probably not because it is so rare, as it is indefinite as compared to adults. Ataxia, disturbances of gait and Romberg's sign are more unusual and the absence of patellar

4. Savy: Quoted by Pehu and Gardere (See Footnote 5).

5. Pehu and Gardere: Arch. de méd. enfants, 1915, xviii, 330.

and Achilles reflexes is not so constant as in adults. The Argyll Robertson pupil is considered a cardinal symptom. Optic atrophy is present in a large percentage of cases and is usually the earliest symptom. The first signs usually appear late in childhood, though cases have been reported as early as 5 and 6 years. In our St. Louis material we have observed but one case, a girl of 18 years, presenting sufficient evidence to make a positive diagnosis. Cases showing diminished reflexes and pupillary changes have not been unusual, and some of these cases might very well be early cases of tabes.

Paresis in children is somewhat more common than tabes, the time of onset being most frequently between the ages of 12 and 16 years. Cases have been reported at 8 years and under, but it is doubtful if it can be diagnosed so early. The characteristic symptoms are both psychic and somatic. In a young child the intellect is not sufficiently developed to show the psychic changes. A positive diagnosis could scarcely be made entirely on the somatic changes, which are merely those of syphilis. The main symptoms, especially as differing from adult paresis, may be summarized as follows: There is arrest of physical and sexual development. The face becomes expressionless. There are automatic sucking, smacking and chewing movements and humming, which rarely appear in the adult. Pupil changes are present early, but they may be merely sluggish instead of fixed. A special peculiarity is the early and frequent occurrence of epileptiform seizures, which have been spoken of as paralytic attacks. The psychic symptoms frequently have a sudden onset. There is a progressive defect in intelligence and judgment, without fixed ideas or hallucinations. Ideas of grandeur, when present, assume an infantile character. The child becomes apathetic, undemonstrative and gradually forgets all that has been learned. Occasionally there are outbreaks of passion, but mania never occurs. There are increasing disturbances of speech, the vocabulary diminishes and speech finally ceases, except a few unintelligible words. Gradually the somatic symptoms become more pronounced and the child becomes bedridden and death results from pneumonia, a paralytic attack, or sepsis originating in decubitis. Remissions, though common in adults, are rare in children. The duration of the disease is usually from three to five years, or even longer. Tabetic symptoms occasionally occur in addition to the paresis. The pathology of juvenile paresis differs but little from that of the adult type, except possibly the greater frequency of cord lesions in the former.

BONES

The most frequent lesion is a chronic osteoperiostitis, gummatous in character, involving chiefly the long bones. It is occasionally seen as early as the second year, but occurs most frequently after the fifth

year. It may occur in any part of the skeleton, but the site of greatest frequency is the tibia. The process as it occurs there is briefly as follows: The shaft of the bone is affected chiefly or exclusively. There appears on the crest a tender, painful swelling, the pain being increased on motion. Roentgen ray shows periosteal thickening over a considerable area, with its greatest thickness at the site of the nodule, where the bone itself is hyperplastic. Necrosis may take place at this site with resulting sinus. In some cases differentiation from tuberculosis offers considerable difficulty. More often the process is arrested without necrosis and a permanent deformity of the bone results, an outward fusiform curving of the involved surface.

Gummas also occur, located centrally in the bone, frequently resulting in bone necrosis with sinus formation. The tibia again is the most common site. The small bones of the hands and feet are not infrequently involved.

There occurs also a diffuse hyperplastic process developing chiefly in the long bones, notably in the tibia. This is usually quite chronic, often continuing over a period of years. The bone may enlarge to twice its normal size, the thickening being due to new periosteal bone layers. The process is not necessarily painful, there occasionally being no pain whatever. When it occurs in the tibia, there is frequently an anterior and occasionally a lateral curving. The disease is usually symmetrical and the deformity permanent. Lengthening of the involved bones is occasionally seen. Syphilitic bone hyperplasia, especially if occurring diffusely at one end of a long bone, may be confused with sarcoma, as in one case in our material. The deformities are differentiated from rickets by the age of onset, the nodular rounded shin, and the increase in size of the bone shaft.

JOINTS

About 10 per cent. of the late hereditary syphilitics show joint affections. Any joint in the body may be involved, though the knee and, secondly, the ankle are affected with much the greater frequency. A striking feature of these affections is their frequent association with eye syphilis. Often these are present at the same time, or one precedes the other by a few weeks.

In going over the literature one is struck by the absence of definite pathologic knowledge, and perhaps for that reason the lack also of a clear-cut clinical classification. Types as described are largely indistinct and one type tends to change to another.

There is the type⁶ described by Clutton of simple symmetrical synovial effusion, chronic in character and without pain. It is insidious

6. Post: Boston Med. and Surg. Jour., 1915, clxxiii, 941.

in its onset and development, the first complaint being a stiffness of the knees and a sense of weight on walking.

There occurs also an acutely developing synovitis, with severe pain and loss of function. This type is without bone involvement as shown by the Roentgen ray and is the variety most frequently found in our material. From its clinical aspect alone it is easily mistaken for a tuberculous arthritis.

A variety frequently seen occurs with swelling of the epiphysis of one or both of the neighboring bones, and gross changes in the joint surfaces. These changes are gummatous in character, involving both the cartilage and bone and are associated with a chronic effusion and a thickened capsule.

A variety not infrequently observed is one resembling the clinical picture of arthritis deformans. The joint involvement is frequently multiple, affecting the small as well as the larger joints. There is a chronic effusion and irregular thickening and lipping of the epiphysis of adjacent bones. There is but little pain and the limitation of motion is merely mechanical.

Tubby⁷ describes a chondro-arthritis, characterized by a recurring synovitis, with chronic inflammation of the neighboring bone. The disease is incurable and he classifies it as parasymphilitic. Joint involvement is more often primary, but it may be the result of extension of pericapsular or bone gummas. In such a case there is often an extensive formation of villi in the joint.

SKIN

Skin manifestations in late hereditary syphilis are largely of two types, a large and small nodular syphilid. The large syphilid is a gumma the point of origin of which is usually in the subcutaneous tissues. On account of its greater frequency this is the most important skin manifestation. It develops most frequently on the face or upper part of the legs and thighs. These lesions are at first indurated, often having a gray color with red borders. They respond quickly to treatment, but if neglected, break down, leaving deep ulcers. The ulcer has a scooped-out appearance, with an indurated border. On healing it leaves a white scar. It is not always easy to differentiate gummatous from tuberculous ulcers.

The small nodular syphilids are pea-size or larger circumscribed infiltrations, later becoming covered with a crust, under which necrosis continues, the whole increasing in size, the center becoming depressed and sometimes becoming serpiginous. The lesion may undergo resolution at any stage, but does not respond so readily to treatment as does the gumma.

7. Tubby: *Brit. Jour. Child. Dis.*, 1908, v, 49.

MUCOUS MEMBRANES

The lesions of the mucous membranes are largely gummatous ulcerations. They occur in the soft palate and pharynx, and gummatous infiltrations are occasionally observed on the epiglottis and in the larynx and trachea. Perforations seen in the soft palate are practically always from this cause. These ulcerations are usually without pain, have sharply defined, indurated borders and on healing leave a smooth, white scar, with a decided tendency to contraction. Adhesion of the soft palate to the pharyngeal wall is sometimes observed.

When gummas occur in the nose or hard palate they may have their point of origin in either the mucous membrane, the bone or the periosteum. In any case the final result, if they are untreated, is the same, either perforation or extensive necrosis of the neighboring bone and soft parts and in the nose causing a protracted ozena. When occurring in the bone there is often considerable pain associated.

EYE

Affections of the eye in late hereditary syphilis are very common and in our material ranked second only to those of the nervous system. The lesion most frequently found is an interstitial keratitis. This affection, though in the great majority of cases being caused by syphilis, is not pathognomonic of that disease. The usual age of occurrence is from 6 to 12 years, though in our own series we have one case at 3 months and another at 20 years. This manifestation, with insufficient treatment, frequently recurs in a few months or years, and from the viewpoint of treatment is often one of the most intractable of the curable affections of syphilis, sometimes requiring several years for cure. Both eyes may be affected at once, or there may be an interval of several weeks or months before the second eye is affected. As Hutchinson pointed out, there is a frequent association between keratitis and Hutchinson's teeth, and in the few cases we have seen having Hutchinson's teeth, this deformity was largely in association with keratitis. The frequent relation to joint disease has been mentioned elsewhere.

A choreoretinitis not infrequently occurs, which is characteristic of syphilis. Gummatous iritis is occasionally observed. Other eye manifestations of syphilis are more properly considered with the nervous system, lesions of which may cause strabismus, nystagmus, optic neuritis, optic atrophy, choked disk, temporary ocular palsies and fixed and unequal pupils.

EARS

Deafness is not infrequently the result of syphilis, and its common association with keratitis has been observed by many, notably Hutchinson. It is usually bilateral and affects girls with somewhat greater fre-

quency than boys. It has been considered as of three types.⁸ The more common type is of insidious onset, without vertigo or other symptoms, complete permanent deafness developing in the course of a few weeks. The lesion is a chronic osteitis, leading to bone proliferation, which gradually more or less completely occludes the cavities of the internal auditory meatus and the bony labyrinth.

In the second variety vertigo is a marked symptom, which is accounted for by increased tension due to exudation. Tinnitus and subjective noises may also be present. With acute onset there is immediate destruction of the labyrinthine nerve endings by pressure alone. If the disease assumes a subacute or chronic course there may be exacerbations with recurring vertigo.

In the third type there is a nerve deafness due to central involvement of the parasyphilitic or central type.

LYMPH GLANDS

Lymph gland involvement as a cause for complaint is uncommon. Such a lesion is usually a gumma, involving either a single gland or a group of glands. These are hard and painless and there is but little tendency to break down. In one such case now under observation the glands have broken down, leaving in the neck an extensive ulceration six inches long.

There is but little tendency to a general adenopathy in late hereditary syphilis, and when this is found it is of no great assistance in the diagnosis.

RESPIRATORY

Affections of the lungs, as manifestations of late syphilis, are rare, and when they occur there are no characteristic symptoms. Large gummas may occur in later childhood, but of more frequent occurrence are small gummatous nodules in infancy. A chronic pneumonia of syphilitic nature has been described, which is followed by bronchiectasis and emphysema. In syphilitic children there is a tendency for all inflammations of the lung and bronchi to become chronic. The number of syphilitic children in our material who have contracted a most intractable chronic bronchitis is striking. The tendency for these children to acquire tuberculosis is well known.

Late manifestations in the larynx, trachea and bronchi are rare. Occasionally gummas occur. We have observed but one case of gummatous ulceration in the larynx. In such a lesion hoarseness and aphonia may be observed. The disease is painless and is diagnosed only by inspection. Untreated, such lesions are prone to cause stenosis from cicatricial contraction. Obstruction from the gumma itself has been observed.

8. Yearsley: *Brit. Jour. Child. Dis.*, 1908, v, 195.

CARDIOVASCULAR

Gross changes in the heart as a result of late syphilis are quite rare. Aortitis, when it occurs, is usually of a syphilitic nature, and aneurysm of the aorta is occasionally observed as a result. Arteriosclerosis is uncommon in children and is usually the result of syphilis. Endarteritis is not often diagnosed clinically, but is a frequent lesion found associated with cerebrospinal syphilis. A syphilitic endarteritis not infrequently causes a symmetrical gangrene of the extremities, one such case having come under our observation.

VISCERA

Visceral involvement is uncommon and, as for its clinical diagnosis, is rare. Splenic enlargement is frequently found, but this is usually a simple hyperplasia, and not a specific change. The spleen may show interstitial changes, either diffuse or circumscribed, and rarely a gumma is found.

The liver is most frequently involved, the lesions being either a gumma or a hypertrophic cirrhosis. Gummas in both the liver and spleen have been described as occurring in earliest infancy.

Chronic interstitial nephritis is said to be due in some cases to syphilis. We have observed what was possibly one such case, though how one can make a positive diagnosis of syphilis as the cause is not entirely clear. Diabetes insipidus has in certain cases been associated with syphilis. Both the adrenal and the testis may show interstitial changes and gummas. There are no important lesions of the stomach or intestine.

MISCELLANEOUS

Paroxysmal hemoglobinuria has been repeatedly described in relation to hereditary syphilis, and it is the opinion of many that it is pathognomonic of this infection. The exact pathology is not yet clear. It is evidently a blood dyscrasia, in which there is an autohemolysis following exposure to cold. The exposure is usually followed closely by a chill and fever. The amount of blood destroyed is usually small and probably corresponds to the amount that is actually chilled during the exposure. The free hemoglobin is rapidly excreted in the urine, 90 per cent. being excreted in the first two hours in an experimental exposure.⁹

Raynaud's disease is not especially rare as occurring in connection with hereditary syphilis. Its etiology and pathology is still unknown, though it is the opinion of many that these symptoms may be caused by syphilis. One case¹⁰ already reported in detail has been seen by us.

9. Dennie and Robertson: *Arch. Int. Med.*, 1915, xvi, 205.

10. Lisser: *Arch. Int. Med.*, 1915, xvi, 509.

DIAGNOSIS

In the diagnosis of syphilis the Wassermann reaction, in competent hands, is invaluable, being positive in practically 100 per cent. of the late cases in childhood.

The value of the family history needs no emphasis. The occasional fact that all knowledge of syphilis is denied by the parents and both give a negative Wassermann has no especial bearing on the diagnosis in the child. Among our cases the father gave a positive reaction in less than 50 per cent. of those tested, even though he was the starting point for the infection in the family. The mother's reaction is positive more frequently.¹¹

The early history of the patient, though helpful, is usually insufficient to make a positive diagnosis. However, some of the early lesions leave their permanent mark. An older child may give a history or show evidence of former lesions of the late type. The various signs and stigmata that may be present will be briefly discussed.

Cutaneous Scars.—Rhagades, or radial scars, about the mouth, the result of syphilitic infiltration in infancy, are produced by nothing else. To be characteristic, however, they must be definitely linear and not limited to the angles of the mouth. The same appearance may be produced about the anus. Old scars of gummatous ulcers usually have a characteristic appearance, being white and smooth and when found on the face or distributed along the tibia are almost positive proof of syphilis.

Mucous membranes may show scars of ulcerations similar to those on the skin. Perforations are usually permanent and are almost invariably due to syphilis.

Disturbances of development are sometimes observed following severe infantile syphilis. These are in no way pathognomonic. The body is undersized, the constitution is delicate and shows but little resistance to disease. Puberty is frequently delayed. Anemia is usually present and the patient has a sallow appearance.

Skeletal Changes.—Teeth: From the standpoint of frequency Hutchinson's teeth is not a valuable sign, though when present constitutes good, but not absolute, evidence of an early infection. The presence of two, widely spaced, instead of four upper incisors is very suggestive, especially if these are pegged or otherwise misshapen. A characteristic deformity of the first molars has been described by Moon.¹² These teeth are "reduced in size and are dome-shaped, through the dwarfing of the central tubercle of each cusp."

11. Jeans: AM JOUR. DIS. CHILD., 1916, xi, 11.

12. Lucas, R. C.: Brit. Jour. Child. Dis., 1908, v, 1.

Head: Cranial bone disease, other than rickets, is rarely due to anything else than syphilis and usually leaves some deformity. There is nothing pathognomonic about the shape or size of the head, though evidence of an arrested hydrocephalus is suggestive.

Nose: Some of the milder grades of pug or saddle nose often prove to be congenital deformities rather than the result of a syphilitic necrosis.

Scaphoid scapulae, though suggestive, have not proved more useful than other disturbances of development.

Tibiae: Thickening and irregularities of the tibiae, especially if these deformities are extreme, make good positive evidence of infection.

Special Organs.—Eyes: Corneal opacities, though in no way a proof of syphilis, are often helpful in connection with the history. Fixed pupils, especially Argyll Robertson pupils, are very characteristic and with but few rare exceptions are pathognomonic. Irregular pupils and synechiae of the iris constitute good presumptive evidence. On ophthalmoscopic examination evidence of a former choroidoretinitis is found in persisting choroidal spots.

Ears: Deafness without obvious destruction in the ear, complete in the course of a few weeks, is almost pathognomonic of syphilis, though from the view point of frequency this occurrence is not very helpful. Syphilitic deafness was present in but 1 per cent. of our late cases, and among several hundred cases of late syphilis Hutchinson's triad occurred not once.

Voice: Swift¹³ has recently directed our attention to a voice sign which has about the same significance as Hutchinson's teeth and scaphoid scapulae. This sign manifests itself in a harsh, rasping, monotonous, low pitched voice that is not amenable to any sort of treatment.

Nervous System.—There are few nervous manifestations pathognomonic of syphilis, but with a progressive acquired mental deterioration or paralysis syphilis is strongly suggested. The occasional occurrence of a positive Wassermann in the spinal fluid when the blood Wassermann is negative must be borne in mind. The Lange colloidal gold reaction is very helpful as a corroborative test, but in its present status syphilis could scarcely be positively diagnosed on that test alone. Other corroborative evidence of value is the presence of globulin and pleocytosis in the spinal fluid.

Rheumatism.—In the presence of vague and persistent affections which are commonly classed as rheumatic, we not infrequently find a rheumatic history lacking and a syphilitic history present. Attention has recently been called to this rheumatic group by several authors.¹⁴

13. Swift: Boston Med. and Surg. Jour., 1915, clxxiii, 619.

14. Stoll: Boston Med. and Surg. Jour., 1915, clxxiii, 606; see also Footnote 3.

The rheumatic pains may be periosteal, bone, muscular or nerve root pains, and are important from the view point of diagnosis, because they yield so readily to proper treatment.

Differentiating Syphilis from Tuberculosis.—This is a point of considerable importance in the welfare of our patients, and one which is not sufficiently appreciated. The difficulty in certain cases of differentiating syphilitic from tuberculous processes is encountered in any part of the body where both diseases tend to manifest themselves, especially in the bones, joints and lymph glands. After the application of all our diagnostic knowledge the nature of the process may still be in doubt or be incorrectly diagnosed. It has been the experience in our clinic¹⁵ that the gross and microscopic pictures of the two diseases may be absolutely indistinguishable. In our opinion, and to a certain extent to our knowledge, many syphilitic processes are treated as tuberculosis, the diagnosis of tuberculosis being supported in some cases by a reliable pathologic laboratory. In such a case a positive Wassermann reaction and the therapeutic test may be our only means of diagnosis.

15. O'Reilly: -Am. Jour. Orthop. Surg., 1914, xi, 431.

A COMPARATIVE STUDY OF THE LUETIN AND WASSERMANN REACTIONS IN INFANCY AND CHILDHOOD *

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In studying the symptoms of congenital syphilis, it is noted that many of the classical symptoms exist in cases which are not syphilitic, and the reverse is also true that cases of syphilis are seen with but few of the classical symptoms. For some time in observing these symptoms one of us (DeBuys) has been impressed with the necessity of using every means available to recognize syphilis early so that the individual may be given the best possible chance in life. In a previous study¹ with the Wassermann reaction before the luetin test was given us by Noguchi, it was shown how the tests compared when made in both mother and child. There were some irregularities which could not then be explained. It is highly probable that many of the irregular cases with negative Wassermann reaction, if they had been examined by means of the luetin reaction, would have been shown to be positive cases of syphilis.

In order to determine the relative value of the serum and skin reactions a systematic investigation was planned. It was hoped that the former series of cases could be examined, but as they were from the outpatient department it was not to be expected that all would be tested. In this series are included as many of the old cases as possible, other cases investigated later and on which there were more than one set of observations, and cases on which only one set of these tests was made.

The complement binding property of the serum was determined both before and after inactivation in a water bath at a temperature of 56 C. for one half hour; the technic when using the active serum was that known as the Tschernogubow modification, as outlined by Gurd, in which the natural hemolysin of human serum against guinea-pig cells constituted the hemolytic system. When using the inactivated serum the technic as originally described by Wassermann was followed rather closely. The antigen used in both instances was the acetone insoluble fraction of an alcoholic extract of a human heart.

* Read before the Section on Diseases of Children at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

* From the Children's Out-Patient and the Pathological Departments of Touro Infirmary, New Orleans.

1. DeBuys, L. R.: A Study of the Wassermann Reaction in Connection with Congenital Syphilis, *AM. JOUR. DIS. CHILD.*, 1913, v, 65.

In the performance of the luetin test the technic as outlined by Noguchi was carried out minutely. Readings were made every forty-eight hours over a period of seven days and as often as possible subsequently.

The study consisted in 350 Wassermann reactions and 100 luetin tests in 175 cases. Only partial investigation could be made in twenty-four patients who did not return for complete observations. In the remaining 151 cases 321 Wassermann and 160 luetin reactions were made. Thirty former patients were included in the study. Among the former patients are considered those who were previously seen and on whom more than one set of observations were made, the period varying from one-half month to five and one half years. Nine of the luetin tests were on those already examined by the same test from one to eight months before. The later readings always corresponding to the previous ones.

There were eighty children, sixty-three mothers and eight fathers included in this investigation. Fifty-four mothers with their children, one child and his father, seven fathers and mothers and children, ten children alone, and two mothers alone. In the latter, in both instances, the Wassermann in the mother and child and the mother's luetin were the same, the child not returning for observation of the luetin reaction.

The children varied in ages from 12 days to under puberty. Forty-two were from 12 days old to under 12 months, and of these thirty-two were less than 6 months; twenty-three others were between 12 months and 7 years, the remaining being distributed from 7 years to 11 years. Seventy-four families were examined. In sixty-two families there were more than one member.

TABLE 1.—DATA CONCERNING PATIENTS ON WHOM THE WASSERMANN AND LUETIN TESTS WERE MADE

	Families	Total
Children alone.....	10	10
Mother alone.....	2	2
Mother and child.....	50	100
Mother and two children.....	3	9
Mother and four children.....	1	5
Father, mother and one child.....	5	15
Father, mother and two children.....	2	8
Father and child.....	1	2
	74	151

TABLE 2.—RESULTS OF WASSERMANN AND LUTIN TESTS ON FAMILIES

Wassermann			Luetin			Instances
Father	Mother	Child	Father	Mother	Child	
+	—	+	+	+	+	1
+	—	—	+	+	+	2
—	+	+	+	+	+	2
—	—	+	+	+	+	1
—	—	—	+	+	+	2
—	—	—	—	—	—	1
—	..	—	+	..	+	1
..	+	+	..	+	+	16
..	+	+	..	—	—	1
..	+	—	..	—	—	2
..	+	—	..	+	+	7
..	—	+	..	+	+	4
..	—	—	..	+	+	26
..	—	—	..	—	—	4
..	—	—	..	2
..	..	+	+	1
..	..	—	+	8
..	..	—	—	1
..	82

* Wassermann made the same day.

TABLE 3.—COMPARATIVE RESULT OF THE WASSERMANN AND LUTIN TESTS

	Wassermann	Luetin	Number
Father.....	+	+	2
Father.....	—	—	1
Father.....	—	+	5
Mother.....	+	+	21
Mother.....	+	—	3
Mother.....	—	—	7
Mother.....	—	+	32
Child.....	+	+	25
Child.....	+	—	1
Child.....	—	+	46
Child.....	—	—	8
			151

* Three Wassermann reactions made on the same day.

† Wassermann made on same day as on No. 5.

TABLE 4.—RESULT OF WASSERMANN AND LUETIN TESTS ON OLD CASES *

First Observation			Later Observation			No. Cases
Child	Mother	Father	Child	Mother	Father	
W+	W+	W+ L+	W+ L+	4
W+	W+	W- L+	W- L+	W- L+	2
W+	W-	W+ L+	W+ L+	2
W+	W-	W- L+	W- L+	W- L+	2
W+	W+ L+	W+ L+	4
W+	W+ L+	W- L+	1
W+	W- L+	W- L+	W- L+	1
W-	W-	W+ L+	W- L+	1
W-	W-	W- L+	W- L+	W- L+	1
W- L+	W- L+	W- L+	W- L+	W- L+	1
W-	W- L+	W+ L+	1
W-	W- L+	W- L+	7
W-	W- L+	1
W-	W- L-	1
.....	W+	W- L+	W- L+	1
.....	30

* W signifies Wassermann, and L, luetin.

It was not possible to read the luetin tests as frequently or as long as desired in all the cases in order to determine the averages for the entire series. Many, however, did as requested, and from them the following was learned:

The shortest reaction in a baby was luetin positive in two days and negative in three days.

The latest positive reaction in a baby was on the eighth day.

The duration of reaction in a child was from two days to fourteen days.

The earliest pustular eruption in a baby was two days; latest, six days.

The shortest reaction in a mother became positive and subsided within three days.

The latest positive reaction in a mother appeared on the twenty-fourth day, close observations having been made in this case at forty-eight-hour intervals. Observations were continued because four of her children gave positive laboratory findings. In another case fourteen days elapsed before the luetin began to light up. In this instance the

mother and child gave marked Wassermann reactions and the child a pustular luetin test.

The luetin test of one mother, after an ordinary positive reaction which was persistent, on the twenty-first day became violently pustular and ruptured. The same occurred in another case on the fourteenth day. To no influencing factor could these reactions be ascribed, such as medicine.

Whether the luetin test influences subsequent Wassermann reactions we cannot say. In two children giving positive luetin reactions, in whom negative Wassermann reactions were obtained on the same day that luetin tests were made, subsequent Wassermann reactions were positive as follows:

On May 6, 1916, a Wassermann and a luetin test were made; the luetin was positive, the Wassermann, both original and Tschernogubow, was negative. On May 18, the Wassermann, both original and Tschernogubow, was again made and was positive.

In an old case on Dec. 7, 1916, the Wassermann was negative; on May 6, 1916, the Wassermann was again negative; the luetin test made on May 6 was positive. On May 20 the Wassermann, both Tschernogubow and original, was markedly positive.

The explanation of this irregularity may be either that the luetin produced a fresh outburst of toxins from the old lesions in the internal organs, thereby stimulating sufficient antibodies to produce a positive Wassermann reaction, or the small amount of dead organisms were sufficient to stimulate antibody formation in demonstrable quantities. At the present writing we have been unable to determine which is the true explanation.

In another case, however, after an interval of twelve days the second Wassermann remained the same, but the previous Wassermann and luetin were both negative.

Some mothers have complained of their children seeming to have a slight fever after the luetin tests were made. In one case, the second of the two cases just spoken of, the child on returning for observation and at the time of the positive Wassermann was not well, having had an upset which could not be explained by any physical or other laboratory examination.

In seven instances in which two luetin tests were made in the same individuals the second luetin reacted more promptly, and in five of these the second reaction was much more pronounced. The interval between the first and second luetin tests ranged from eight days to eight months. The intervals in the five pronounced second reactions were from one month to eight months. The other two were eight days and two months, respectively.

The effect of the iodids on the cases after a sufficient time had elapsed for a decidedly negative reading was negative. The iodids given in positive cases seemed to prolong their positive readings. No attempt was made to determine the effect of the administration of the iodids before the luetin tests were made. In this connection, the most violent positive luetin reactions in the series of this paper were in a mother and nursing baby in both of whom there was not the slightest evidence of syphilis. The mother, however, had some rheumatic pains, which she attributed to exposure. Needless to say, the surprise was indeed great. It developed later that the mother had been given potassium iodid in the adult service for rheumatism and was taking fifteen grains three times a day. The interesting feature in this instance was the effect of the administration of the iodids to the mother on the luetin reaction, not only in herself, but her baby. The discontinuance of the iodids caused a magic subsidence in the luetin reaction of both mother and child, and a return to the administration of the iodids to the mother produced a relighting of the luetin test in both.

WASSERMANN VERSUS LUETIN

In this study the luetin reaction appears to be vastly more reliable for determining the existence of syphilis than the Wassermann.

Table 2 shows that in the eighty-two children and parents, in all but three instances, the reading of the luetin tests was dependable, not being negative in any member of a family in which a member of the family gave a positive luetin. In the three families giving negative luetin tests with positive Wassermann reactions the following is to be said: In two instances the Wassermann reactions of the babies and the luetin tests in the babies and mothers were negative, and only the Wassermann reactions in the mothers were positive. These two Wassermann reactions were very positive and were made on the same day, but not the same day the babies' Wassermann tests were made. In the third instance the Wassermann reactions in the baby and mother were both positive and the luetin tests in both mother and baby were negative. These two Wassermann reactions were very positive and were made on the same day as were those in the other two cases just mentioned. These four constitute the only instances in this series in which the Wassermann reactions were positive and the luetin tests negative, and we believe this to be due to an error in technic and not to an error on the part of the luetin, as these all occurred on the same day and in cases that could not clinically be considered syphilitic. Attempts to secure control Wassermann reactions were unsuccessful.

In the remaining seventy-nine instances the reading of the luetin in the child was a reliable guide to the existence or nonexistence of syphilis in the family. In none of these cases was a negative luetin

found in either parent if a positive luetin was found in the child, and with the exception of three instances looked on as errors, a negative luetin in the child was not found in any instance with a positive Wassermann in the child or with either a positive Wassermann or luetin in either parent, or brother or sister.

In the parents, whenever there existed positive Wassermann reactions, there were found positive luetin reactions, and in many instances in which there were negative Wassermann reactions there were found positive luetin reactions.

It is interesting that the luetin reactions ran uniformly in families. Either they were all positive or all negative.

In Table 3 the comparison of the Wassermann and luetin reactions is shown in the individuals. The more accurate reading of the luetin test is again evident. The same four exceptions appear in this tabulation.

Table 4 shows the old cases. These old cases had been previously studied with the Wassermann only, except in one instance. Had these cases been formerly studied by only the Wassermann in the child alone, thirteen cases out of twenty-nine would not have been recognized.

In the eight instances in which the former Wassermann reactions in the mothers were negative had no other observations been made, in all of them syphilis would have been excluded.

The Wassermann reaction may vary from time to time owing to the activity or inactivity of syphilis in the individual. In six instances in the child the former and later reaction were positive on one occasion and negative on the other. And in eleven instances the Wassermann reactions were negative on both examinations in the child and the luetin reaction gave positive findings, not only in the child on one occasion, but in one or both parents in the remaining ten instances.

In every instance in which the Wassermann was positive in either the mother or child the luetin reaction was invariably positive, not only in the child, but also in all the parents tested.

CONCLUSIONS

1. The Wassermann reaction is not so valuable as the luetin test in cases of hereditary syphilis.

2. Our series shows that it is impossible for a mother to give birth to a child who gives positive laboratory tests for congenital syphilis without herself giving positive tests.

3. While we believe that the luetin test is of more value in being more often positive than the Wassermann, we do not believe that it should displace the Wassermann, as both tests, it would seem, serve distinct purposes, the Wassermann to give evidence of the presence of

antibodies in the circulation, indicating an active process; while the luetin not only gives this evidence, but also indicates an existing syphilitic condition, even though it be inactive.

4. The luetin test is not without its disadvantages, as it requires considerable experience in differentiating the lesion from the simple reaction produced by the intradermal injection of sterile inert foreign material. It is also influenced by the administration of certain drugs, which may give rise to a pseudoreaction, thereby adding to the possible inaccuracy in the interpretation of its reading.

5. Luetin reactions should not be considered negative until sufficient time shall have elapsed to warrant such a reading.

Our sincerest thanks are due Dr. Hideyo Noguchi for supplying us with luetin for this study, and to Drs. J. F. Baldwin and Ruffin T. Perkins for their valued assistance.

TREATMENT OF HEREDITARY SYPHILIS *

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The status of the treatment of hereditary syphilis is today not wholly unlike that of adult syphilis. Up to seven or eight years ago mercury and its salts and potassium iodid had for four hundred years or more done fairly well in all except the very severe cases, in which the patient died. The "cure," as they called it then, or the disappearance of symptoms and visible lesions was slow, often requiring months and years. The perfection of the Wassermann reaction and its intelligent application to treatment, as well as to diagnosis, gradually broadened our conceptions as to the problems of the disease and brought sharp realization that our clinical cures were so in name only and that far longer periods of treatment and observation were necessary. This sane attitude was greatly influenced by the widely heralded appearance of the patented arsenical preparations. Here was the long-sought-for cure, short, safe and easy, with little bother to parent or doctor, one or two injections only and the child was well! These articles were received and used with enthusiasm only slightly tempered with caution. The literature immediately blossomed, in fact became all cluttered up, with glowing reports of cures based on a few patients treated by one or two doses or observed for only a short time. There were deaths, to be sure, but very few of them could be traced directly to the disease or the cure. Gradually, however, it was noticed that the cured patients did not stay cured and that clinical relapses followed as a rule the cessation of treatment.

The war put a stop to the importation of arsenicals and made us look around for other forms of treatment. It also gave us an opportunity to take a long breath and review the accumulated experience in a saner mood, digest it and apply the results to our cases with caution and common sense. The general feeling today is that the arsenicals, while producing almost miraculous immediate results, do not cure, and that successful treatment, far from being short and simple, is long and complicated and depends on the intelligent application of a combination of drugs to the type of case treated.

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* From the medical service of the Children's Hospital, Boston.

With the new light thrown on pathologic conditions by the Wassermann reaction it has become convenient to divide for the purpose of treatment congenital or hereditary syphilis into the following four types:

1. Fetal, that is, intra-uterine.
2. Early infantile, secondary, or inflammatory, in which the lesions are largely mucocutaneous and visceral, frequently osseous, and occasionally nervous, occurring through the first year of life.
3. Tardy, late, tertiary, or hypertrophic, in which the lesions are largely osseous, nervous and gummatous.
4. Latent, in which the only direct evidence of syphilis is a positive Wassermann reaction.

The second and the third type overlap considerably and may have several sets of lesions in common.

TREATMENT

Fetal.—Common sense would indicate that a pregnant syphilitic woman would have a better chance of giving birth to a viable child if she were effectively treated than if untreated. While little has been written on this phase in this country, I know that it is the custom in Boston and other cities which have pregnancy—or prenatal-care—clinics to treat pregnant syphilitic women; that the general feeling is that the treatment does no harm, that the mothers are very much benefited, that there are fewer pregnancies terminated by abortion or stillbirth, and that the percentages of viable children are greater. Abroad Meyer¹ and others² have treated numbers of pregnant syphilitics and have concluded that vigorous treatment does the mother no harm and increases tremendously the percentage of viable children born. In Boston Huntington³ tells me that every pregnant woman coming into the pregnancy clinic of the Boston Lying-In Hospital is required to have a Wassermann test. All showing a positive reaction are referred to the Massachusetts General Hospital for active anti-specific treatment. He states positively—but is not in a position to give figures—that not only is the percentage of viable children very much increased, but that very few new-born children of treated syphilitic mothers show manifestations of syphilis. Williams⁴ and others⁵ show that the greatest single influence in fetal mortality is syphilis.

1. Meyer, E.: München, med. Wehnschr., Aug. 18, 1914, lxi, 1801.

2. Sauvage: Quoted by E. Meyer (see Footnote 1). Fabre and Bourret: Lyon méd., 1912, cxix, 716. Galliot: Arch. de méd. d. enfants, 1913, xvi, 892. Findlay and Robertson: Quart. Jour. Med., 1915, viii, 175.

3. Huntington, J. L.: Personal communication to the author.

4. Williams: Tr. Am. Soc. Prev. of inf. Mort., p. 46.

5. Jeans and Butler: AM. JOUR. DIS. CHILD., 1914, viii, 327.

estimating that from 26 to 40 per cent. of all fetal accidents are due to that cause alone and recommending the earliest possible active maternal antisyphilitic treatment. Others,⁶ however, while writing in much the same vein, believe that maternal treatment should be undertaken with caution and cite instance of severe fetal accidents apparently due to maternal treatment.

Early Direct Treatment.—Experience has shown that inasmuch as the Wassermann reaction is negative at birth in so many children of known syphilitic parentage,⁷ clinical evidence should override the negative Wassermann in the new-born and treatment be instituted at once.⁸ Owing to difficult and complicated technic as well as to reported serious by-effects, salvarsan has largely been discarded, except in very small doses.⁷ The feeling is now general that neosalvarsan, owing to ease of administration, simple technic and lack of harmful by-effects, is preferable to salvarsan, but that its effect is not so impressive or so lasting. Further, most of the observers⁹ conclude that none of the arsenicals alone cure, even with prolonged and frequent use; that while clinical evidence disappears almost magically and remains in abeyance as long as arsenic is administered, yet in only a few weeks after cessation of arsenic, symptoms again become manifest. These observations and the scarcity of salvarsan and neosalvarsan, as well as the lack of adequate experience with the new American arsenicals, diarsenol and arsenobenzol, have led to a reaction favoring the old treatment by mercury and the feeling that arsenic is useful at first and in acute phases, but alone is insufficient, that it must be accompanied by mercury in some form. Some¹⁰ believe that mercury first, for a short time, prepares the way for an intensified action by arsenic and diminishes its dangers. Recent opinion seems to favor mercury by inunction, or mercury with chalk over other mercurial preparations and the inunctions appear to be more popular than the mercury with chalk.

The question of the dose of salvarsan or neosalvarsan has been pretty well threshed out without definite decision, some claiming that the dose of from 0.01 to 0.015 gm. salvarsan, or from 0.015 to 0.02 gm. neosalvarsan per kilogram body weight is too small to give the best effect, and lay clinical failures to the smallness of the dose. Others feel that the dose is too large and fraught with danger, but not very effective. Most¹¹ agree, however, that the dose should be given in concen-

6. Lemeland and Brisson: Arch. mens. d'obst. et de gynéc., Paris, 1913, cxiii, 256. Dupérie: Gaz. hebdomadaire de médecine et de chirurgie, 1913, xxxiv, 87.

7. Bunch: Brit. Jour. Child. Dis., 1914, xi, 297.

8. Steinert and Flusser: Arch. f. Kinderh., 1915, lxxv, 45.

9. Dunzelman: Ztschr. f. Kinderh., 1913, v, 512.

10. Hoffman: Dermat. Ztschr., 1914, p. 508.

11. Blechman: Paris médical, 1913-1914, xiii, 205. Holt and Brown: Am. Jour. Dis. Child., 1913, vi, 174.

trated solutions intravenously at any accessible vein, the veins of the neck or scalp being most favored. In cases in which the veins are so small or for other reasons attempt at intravenous medication seems inadvisable, injections through the longitudinal sinus according to the method of Marfan and Helmholtz¹² is ridiculously easy. The ingenious head-holder which Helmholtz has designed has in our experience proved unnecessary.

Most observers agree that the arsenicals should be supplemented by mercury in some form, such as inunctions, mercury with chalk, mercurous chlorid, mercuric chlorid, and mercurous salicylate by mouth or by intramuscular injection. One of the most experienced¹³ favors topical applications of mercuric chlorid to the moist lesions while neosalvarsan is being administered and gives 2 mg. of mercuric chlorid intramuscularly once a week following. Another¹⁴ gives twelve injections of mercurous chlorid 0.001 gm. per kilogram followed by eight doses of neosalvarsan 0.015 per kilogram, followed by twelve doses of mercurous chlorid again. He also replaces at will the mercurous chlorid by inunctions of mercury. He believes that this series of treatment should be repeated every few months. Others¹⁵ prefer mercury with chalk to supplement the arsenicals, in doses of one-half to one and one-half grains three times daily for from two to six weeks, then omitting for from one to three weeks and repeating.

As to arsenicals other than salvarsan and neosalvarsan, diarsenol (Canadian salvarsan) has apparently been used but little among children; what experience is available from its use among adults would place it parallel with salvarsan, except that it is liable to become decomposed more readily, causing disquieting by-effects,¹⁶ and is recommended to be used in doses slightly smaller than salvarsan. Arsenobenzol, introduced by Schamberg, is similar to salvarsan. Dr. Schamberg¹⁷ states that he gives from 10.0 to 15.0 mg. in 1.25 c.c. sterilized liquid petrolatum containing a drop or two of beechwood creosote. He advocates from 4 to 6 mg. per kilogram body weight. He injects deeply into the gluteal muscles, and states that the injection causes very little pain. He reports satisfactory results. This method apparently presents at least the advantage of simplicity over the complicated technic of the salvarsan type of intravenous administration. Salvarsan sodium or

12. Helmholtz: *AM. JOUR. DIS. CHILD.*, 1915, x, 194.

13. Baginsky: *Therap. d. Gegenw.*, 1915, lxvi, 67.

14. Mueller: *Berl. klin. Wchnschr.*, 1915, lii, 1034.

15. Veeder and Jeans: *AM. JOUR. DIS. CHILD.*, 1916, xi, 177. Smith: *Boston Med. and Surg. Jour.*, 1916, clxxxiv, 198. Cook: *Jour. Am. Med. Assn.*, 1916, lxvi, 865.

16. Ormsby and Mitchell: *Jour. Am. Med. Assn.*, 1916, lxvi, 867.

17. Schamberg: Personal communication to the author; also *Jour. Am. Med. Assn.*, 1915, lxv, 1387.

salvarsan natrium,¹⁸ as recently advocated for adults, is as simple to administer as neosalvarsan. I find no record of its use among children.

In addition to the above, there are certain startling, really new, ideas, such as the use of antimony,¹⁹ quinin,²⁰ tuberculin,²¹ to induce fever, and an unusual but not necessarily valuable contribution is that of administering mercury vapor by inhalation.²²

Indirect Treatment.—Practically all observers agree that most syphilitic babies get along better when receiving their mother's milk than when artificially fed. A good deal has been said, much has been done, but very little proof has been adduced that breast milk alone from a treated syphilitic mother materially influences the lesions in her nursing. Arsenic or mercury has been found in such breast milk in only minute traces by one or two observers,²³ but Ehrlich himself believes the benefit following this method to be due to the excretions of antibodies in the milk, these having been set free in the mother by the destruction of the spirochetes; but he says the effect on the child is uncertain. Others feel that the effect lies wholly in the better quality of the milk owing to the improved general condition of the mother. Salvarsanized serum²⁴ has been injected by some, but with unsatisfactory results.

Briefly, then, a hypothetical patient would receive the following treatment:

First, during pregnancy its mother would be treated vigorously.

Second, at birth, whether showing lesions or not, or whether having a positive Wassermann reaction or not, it would receive inunctions of 25 per cent. mercurial ointment for about two weeks, during which time, if lesions occurred, or if the patient got worse, it would immediately receive 0.15 or 0.2 gm. neosalvarsan in 5 c.c. distilled water, intravenously, at weekly intervals, meanwhile continuing the mercury. As soon as the lesions disappeared the neosalvarsan would be stopped and the mercury alone would be continued for several months, except for temporary cessation made advisable by the appearance of a mercurial diarrhea. At six months a Wassermann test would be made, and if positive, mercury would be continued as above. If negative, mercury should be given intermittently about half the time, that is to say, every other week or every other fortnight, but should not be omitted for

18. Wechselman and Dreyfus: *München. med. Wchnschr.*, 1915, lxii, 6.

19. Brandweiner: *Wein klin. Wchnschr.*, 1916, xxix, 26.

20. Breitman: *Therap. Monatsh.*, 1914, xxviii, 504.

21. Black: *Wien. klin. Wchnschr.*, 1915, xxviii, 49. Luithlen: *Ibid.*, 1915, xxviii, 1421.

22. Frankensein: *Deutsch. med. Wchnschr.*, May 13, 1915, No. 20; abstr. *Jour. Am. Med. Assn.*, 1915, lxxv, 60.

23. Simpson and Thatcher: *Brit. Med. Jour.*, 1913, ii, 534.

24. Meirowsky and Hartman: Quoted by Simpson and Thatcher in quoting Jeanselme (Footnote 23).

longer than a fortnight. At $1\frac{1}{2}$ years a Wassermann test should be made, but the result should have no influence on the treatment. At 2 years treatment may be stopped if the Wassermann reaction is then negative, and if again negative at $2\frac{1}{2}$ years the patient may be considered tentatively cured. Many believe,²⁵ however, that the Wassermann should be made more frequently and over a longer period than this. Others believe that neosalvarsan or some other arsenical should be given every two, three, or four months. Many believe that an apparently cured patient should be kept under observation for several years and a Wassermann test made at intervals of from six months to a year.

Treatment of Tardy, or Late, Types.—To a certain extent, manifestations of early and of late syphilis overlap. As a matter of fact, there is no clear-cut distinction in the lesions other than the time of their appearance; that is to say, some early cases present manifestations more often seen in later syphilis, and, conversely, some late cases present lesions usually seen in the early stage. For example, many bone lesions are seen very early; occasionally lesions of the nervous system are seen very early, and conversely. Ordinarily late cases may be divided into two groups, the first presenting lesions in bones, joints, eyes and teeth, developing gummatas, and producing general malnutrition, that is, corresponding pretty closely to what we used to call the tertiary stage of adult syphilis. It appears to be the feeling that late or tardy syphilis represents an essentially mild infection, or the results of an insufficiently treated earlier stage, in which results of treatment are more encouraging than in the adult, but less so than in the early stage, and it seems also that the arsenicals are not so urgently needed, but that patients do better with them than on mercury alone.²⁶ This feeling is not borne out by our experience at the Children's Hospital. The second group represents lesions of the central nervous system. In cases of early cerebral involvement corresponding to what we call syphilitic meningitis and encephalitis, hydrocephalus, usually accompanying mucocutaneous lesions, mercury and potassium iodid were held to be pretty ineffective. But treated as cases of ordinary early syphilis, that is to say, with arsenic and mercury, the lesions clear up fairly rapidly. While the truly late cases of cerebral involvement, idiocy, epilepsy, late hydrocephalus, paralysis, etc., are possibly more responsive to treatment than corresponding adult cases, yet they are susceptible to only little improvement, whether treated along the later lines or treated for acute general syphilis.²⁷

25. Boardman: Jour. Cutan. Dis., 1914, xxxii, 545.

26. Yerington and Holsclaw: AM. JOUR. DIS. CHILD., 1914, vii, 32. Strathy and Campbell: Ibid., 1913, vi, 187. See also Footnote 15.

27. Jeans, P. C.: Personal communication to the author.

While little has yet been published on this particular phase, some feel that experience with adults would lead to the belief that direct treatment of the nervous system by the Swift-Ellis technic, or other intraspinous application, would have positive results. Others²⁸ conclude that patients not responding to intravenous or other general treatment are not benefited by intraspinous treatment. Walker,²⁹ however, reports among other cases, that of a child of 3 years with syphilitic meningitis, who received no benefit from general antisyphilitic treatment. He was then given in all four doses of salvarsan, 0.2 gm., and also nine intraspinous injections of salvarsanized serum, undiluted, and mercurial inunctions, following which blood and spinal fluids became negative and cell counts normal. After four months the child was apparently normal, except for deafness.

Again, Leopold³⁰ cites three patients with late syphilis, with manifestations in bone, viscera and central nervous system, distinctly improved as to mental condition following intensive treatment by arsenic and mercury. One patient received a dose of salvarsanized serum intraspiously. Post³¹ tells me that he believes patients with syphilis even of the central nervous system, are improved by general treatment with arsenic and mercury.

Latent Syphilis.—Strictly speaking, latent syphilis is syphilis in which the only manifestation is a positive Wassermann reaction. Nevertheless, the Wassermann test has brought us to the conclusion that many cases of backwardness, malnutrition, underdevelopment and mental retardation, presenting no lesions whatever of syphilis, are really cases of syphilis in which the infection has never gotten under way. Such cases are usually in older children, not necessarily sick, but distinctly under par in one or several ways. The spleen is not necessarily enlarged, although it often is so. A careful and tactfully taken history will bring up a strong probability of parental syphilis. The Wassermann reaction is positive, justifying the routine employment of this reaction in all cases in which the condition is not ordinarily satisfactorily explained.³²

Surprisingly little has been done here or abroad in the study or treatment of this condition. Common sense would indicate that treatment is advisable, and experience would justify the belief that one or several doses of arsenic might produce a provocative reaction³³ or

28. McIntosh, Fildes, Head and Fearnside: *Brain*, No. 36, p. 1. Fildes and McIntosh: *Ibid.*, p. 236.

29. Walker, I. C.: *Boston Med. and Surg. Jour.*, 1916, clxxiv, 195.

30. Leopold, Jerome Sam: Personal communication to the author.

31. Post, Abner: Personal communication to the author.

32. Post, Abner: *Boston Med. and Surg. Jour.*, 1914, clxx, 11.

33. See Footnote 26, second reference.

mobilize the spirochetes and bring them within the reach of further treatment.³⁴

Dangers of Treatment.

1. Of mercury. In a gathering of this sort little need be said about the untoward effect of the excessive or too long use of mercury. Outside it still seems to be very little realized that salivation and gingivitis occur only in the presence of teeth, and that the symptom most to be watched for is a diarrhea not accounted for by the child's feeding or by its general condition.

2. Arsenic. Very few cases of evil effects directly attributable to arsenic have been reported lately. Most of the so-called "salvarsan deaths" were due to hemorrhagic encephalitis and nephritis. It is believed that many of the severe reactions are caused not so much by the arsenic as by the endogenous toxins liberated by so many dead spirochetes. The less serious by-effects are vomiting, fever and bloody

34. The following references are not directly quoted in this paper, but they will be found of value for the purpose of weighing evidence or of indicating the balance of opinion:

- Jeans: Familial Syphilis, *AM. JOUR. DIS. CHILD.*, 1916, xi, 11.
 Neff, F. C.: *Mo. State Med. Assn. Jour.*, St. Louis, xii, 338.
 La Fetra: *New York State Jour. Med.*, 1916, xvi, 3.
 Steiner: *Med. Rec.*, New York, April 24, 1915, lxxxvii, 705.
 Rostenberg: *Med. Rec.*, New York, 1915, lxxxvii, 9.
 Ogilvie: *Jour. Am. Med. Assn.*, Nov. 28, 1914, lxiii, 1936.
 Heidingsfeld: *Ohio State Med. Jour.*, 1914, x, 11.
 Findlay and Robertson: *Glasgow Med. Jour.*, 1914, lxxxii, 6.
 Elias: *South. Med. Jour.*, 1914, vii, 708.
 Schamberg, J. F.: *Jour. Am. Med. Assn.*
 Corbus: *Illinois Med. Jour.*, 1914, xxvi, 2.
 Fildes and McIntosh: *Brain*, No. 37, p. 191.
 Andronescu: *Deutsch. med. Wchnschr.*, 1912, xxxviii, 761.
 La Fetra: *Arch. Pediat.*, 1912, xxix, 654.
 Von Bokay: *Wein. klin. Wchnschr.*, 1911, xxiv, 583; *Arch. f. Kinderh.*, 1913, lx, lxi.
 Baginsky: *Festschrift*, p. 107.
 Wechselmann: *München. med. Wchnschr.*, 1915, lxii, 1638.
 Best: *Med. Rec.*, New York, 1916, lxxxix, No. 11, p. 473.
 Rytina and Judd: *Am. Jour. Med. Sc.*, 1915, cxlix, 2.
 Wolf: *New York State Jour. Med.*, 1916, xvi, 1.
 Thompson: *Jour. Am. Med. Assn.*, 1915, lxiv, 18.
 Mott: *Brit. Med. Jour.*, Jan. 30, 1915.
 Pedersen: *New York Med. Jour.*, 1915, ci, 2.
 Corbus: *Jour. Am. Med. Assn.*, 1914, p. 550.
 Fordyce: *Jour. Am. Med. Jour.*, 1914, p. 552.
 Riggs: *Jour. Am. Med. Assn.*, 1915, p. 840.
 Swift: *Jour. Am. Med. Assn.*, 1915, p. 209.
 Hoffman: *Deutsch. med. Wchnschr.*, 1914, xl, 1168.
 Werther: *Deutsch. med. Wchnschr.*, 1914, xl, 1099.
 Schmitt: *München. med. Wchnschr.*, 1914, lxi, 1337, 1396.
 Saphier: *Wien. klin. Wchnschr.*, 1914, xxvii, 1058.
 Krefling: *Deutsch. Med. Wchnschr.*, 1915, xli, 979.

diarrhea. I was impressed in going over the literature as to the salvarsan deaths with the large number of patients reported as dying of pneumonia two or three weeks following salvarsan treatment. It seems to be the general feeling that arsenic should not be used in cases of nephritis or of cardiac disturbance.

In the Children's Hospital in Boston we have treated a few over one hundred patients with hereditary syphilis in the last two years. Of these, fifty-eight have now developed enough clinical evidence to be of value. We have naturally treated no fetal patients. Of the second, or early type, we have treated fifty patients, most of them coming in when under 6 months old; of these, eighteen, presenting clinical evidence of early syphilis, positive Wassermann reaction, but not seeming acutely sick, received mercury alone, thirteen by inunction, five receiving mercury with chalk. None died and all did fairly well, were clinically free from signs in from two to six months (none under two months), and only two now have a negative Wassermann. These have been treated for over a year and a half. All who have been treated for more than six months seem to be as healthy as the average baby. At first we treated all patients with neosalvarsan, but as the drug became scarce and costly we reserved it for use on those who were very sick and who we felt would die within a few days on mercury alone. Of the seventeen patients so treated only four died, one two days, one five days and two between two and three weeks after treatment, who did not return to the hospital as directed. These latter two deaths were apparently from bronchopneumonia. The remaining thirteen of these seventeen desperately sick babies are now, after a period of months, as well as the average baby. Only eight of them, however, have a negative Wassermann; only one of these eight has been treated for less than six months. Nine other patients not desperately sick were treated by neosalvarsan and mercury. In them the effect of the neosalvarsan was even more rapid than in the desperately sick children in causing the disappearance of mucocutaneous lesions. Of those nine, seven, now treated for nearly two years, have had two negative Wassermann tests three months apart.

Our maximum dose of neosalvarsan has been 0.4 gm. in babies of $1\frac{1}{2}$ years or over. At 1 month or under we give 0.1 gm.; from 1 to 6 months, 0.2 gm.; from 6 months to a year, 0.25 gm., and from 1 year to $1\frac{1}{2}$ years, 0.25 to 0.35 gm. We give the neosalvarsan intravenously in 5 c.c. freshly distilled water, and repeat the dose weekly until all evidence of syphilis except the Wassermann reaction has disappeared. In all cases in which it has been possible the baby has been breast fed and the nursing mother has received treatment

at other hospitals. Our largest number of injections of neosalvarsan was seven, in which case the dose was from 0.05 to 0.075 gm., which I believe to be altogether too small. There were five patients, however, who received only one dose, varying from 0.1 to 0.2 gm., and they presented no visible lesions except pigmentation at the end of from three to seven days. All the patients receiving neosalvarsan were started on mercury on the same day. Most of the patients receiving neosalvarsan were clinically well within one month.

A word as to prognosis in this type of case. Our experience does not justify the pessimistic attitude of Veeder and Jeans and others who report an ultimate mortality of about 40 per cent. and a morbidity of about 60 per cent. Our immediate deaths were four; our ultimate deaths have been none. Our morbidity, in patients treated long enough to count, is practically nil. These children are not even backward and are a fine-looking lot of babies. This is quite in contrast with a series of twenty consecutive patients admitted to our hospital wards and treated before the advent of arsenic. These were necessarily severe cases. Of these twenty patients with severe syphilis, sixteen died within two months, one is living and three cannot be found.

Of the late type of case, we have treated eight patients, varying from 4½ to 9 years old. Four, who were treated with mercury and potassium iodid, showed some improvement and all have positive Wassermann after periods of treatment of from six months to two years. Four have been treated by neosalvarsan and mercury and have improved tremendously in general physical condition within a month after receiving neosalvarsan, but still have a positive Wassermann and the mental condition has failed to reach normal, although considerably improved. We feel that neosalvarsan, while not wholly effective in this condition yet offers more hope of improvement than the older remedies. We have used no intraspinal medication, believing that the nerve men were more qualified than we to carry out this procedure.

Latent Cases.—We have to date treated only five cases corresponding to the latent type. (These are not included in the fifty-eight cases reported above.) Four of these have received neosalvarsan as well as mercury. Their mothers say they are brighter, “do not act so queer” and are much livelier. All of them have gained more rapidly in weight than before treatment was undertaken. The one receiving mercury alone has also improved and gained in weight. They have, however, been under observation and treatment for too short a time to present evidence of value.

CONCLUSIONS

1. Fetal syphilis should be treated by treating the pregnant syphilitic mother vigorously. The balance of evidence shows that the child is much benefited thereby.
2. Arsenic should be used in fairly large doses if immediate intense action is desired.
3. Mercury in one form or another should be used in conjunction with arsenic and continued a long time after all evidence of the disease has disappeared.
4. Treatment should be persisted in for at least two years, after which a negative Wassermann, after six months without treatment, may be considered evidence of a cure.
5. Neosalvarsan appears to be the most favored arsenical.
6. Lesions other than of the central nervous system may be readily relieved.
7. To date the therapy of the lesions of the central nervous system is disappointing but not discouraging.
8. Latent cases should be treated.

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PROGRESS IN PEDIATRICS

A REVIEW OF THE LITERATURE OF SYPHILIS IN INFANCY AND CHILDHOOD *

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Since the last Review slight advances have been made here and there but, as a whole, our conception of syphilis has been changed but little. The same questions are debated and the same conflict of opinion is manifest. It is not the purpose of this review to notice every article published, but rather only so many as will serve to demonstrate efficiently the trend of present thought. Nevertheless, the general plan of the previous review has been adopted without other alteration.

SOLUTIONS FOR INJECTIONS

On the whole, the ancient methods of preparing the arsenical remedies for injection still prevail. The only noteworthy modification is Taege's¹ method of procuring an absolutely sterile salt solution. He first rids the water of any calcium, magnesium, manganese or iron which it may contain by adding an alkali, allowing the mixture to stand twenty-four hours and then filtering. The glass or crockery vessel to be used is scrubbed out with strong hydrochloric acid. Then a mixture of 2.5 gm. strong, hydrochloric acid and 1 gm. sodium chlorid is poured in. Next, a 1 per cent. alcoholic solution of phenolphthalein and a solution of sodium chlorid are added, drop by drop, until a distinctly pink color is produced. A sterile normal salt solution results which will keep for months without change, uncovered. The salvarsan can be dissolved easily in the acid solution and later can be neutralized, avoiding, however, overalkalization in the process.

THE THERAPY OF SYPHILIS

Passing to the consideration of the therapy of syphilis, we shall find no such comparative agreement. The dosage, the therapeutic indications and the method continue to be much disputed.

Dreyfus² advises the employment of salvarsan in from 1 to 1.5 per cent. solution.

* Submitted for publication June 7, 1916.

1. Taege: München. med. Wchnschr., lxi, 1325.

2. Dreyfus: Deutsch. med. Wchnschr., lxii, 178.

Schmitt* advocates, by implication, concentrated solutions. He says that according to the evidence there is danger in submitting a diseased circulatory apparatus to the sudden strain of the dilute solution with its consequent increase in the bulk of the circulating medium.

Simon³ recommends the cautious administration of small doses of salvarsan in old syphilis, incompletely or carelessly treated with large doses at some previous time, in cases of secondary syphilis, and in cases in which meningitis has been demonstrated by lumbar puncture. Otherwise a troublesome and even fatal Herxheimer reaction may be excited. He reports a case in which the reaction caused a fatal edema of the glottis. Simon says 0.2 gm. is an average primary dose for adult patients. If the temperature or the spinal fluid shows no ill effects, subsequent doses may be gradually but cautiously increased.

Nicholas and Mutot⁴ agree with Simon that the initial dose of salvarsan should be small and that subsequent doses should be increased gradually and cautiously. They calculate the normal dose on the basis of 0.01 gm. salvarsan, or of 0.015 gm. neosalvarsan, to each kilogram of body weight. The maximum dose of salvarsan however, should not exceed 0.6 gm. and of neosalvarsan, 0.9 gm. Two courses of five or six injections each, one injection each week, may be employed, the second course commencing one or two months after the first.

Leir's⁵ abortive method consists of the combined use of neosalvarsan and of a soluble mercurial salt. He first injects the mercurial and, a little later, the neosalvarsan. This preliminary treatment is followed by weekly injections of neosalvarsan for five or six weeks, and by about twenty injections of mercury salicylate at two or three day intervals. If possible the primary sore is excised or at least cauterized. In secondary syphilis he advocates weekly injections of from $\frac{1}{2}$ to 1 per cent. suspensions of mercury salicylate or, if the tonsils show signs of recurring disease, of the bichlorid or succinamid.

Krefting⁶ believes in large doses of salvarsan. Three to five injections, he says, given at intervals of two weeks, will cure primary syphilis. In secondary syphilis eight to fifteen doses may be required. No rule of treatment can be formulated, however, save that it must not stop with the production of a negative Wassermann. In his opinion salvarsan therapy has no contraindications.

* Footnote 10.

3. Simon: *Canad. Pract.*, xxxix, 655.

4. Nicholas and Mutot: *Ann. de dermat. et de syph.*, 1914, Series 5, iv, 391.

5. Leir: *München. med. Wchnschr.*, 1914, lxi, 2333.

6. Krefting: *Deutsch. med. Wchnschr.*, 1915, xli, 979.

7. Hell: *Deutsch. med. Wchnschr.*, 1915, xli, 787.

Hell⁷ is convinced that the most efficient method of treating congenital syphilis is by combining inunctions or intramuscular injections of mercury with intravenous injections of salvarsan. He insists, however, that it is important to add to this treatment hygiene and breast milk feedings. He uses either daily inunctions of mercury for from four to six weeks, with a bath after every sixth treatment, or biweekly injections of from 0.003 gm. to 0.005 gm. of the bichlorid (mercuric chlorid 1, sodium chlorid 10, distilled water 100). The mercurial course is followed by a series of four or five weekly intragluteal or intravenous (into the temporal vein) injections of from 0.005 gm. to 0.15 gm. of neosalvarsan in concentrated solution. A second combined course is given a few months later, succeeded, perhaps, by a third or even by a fourth. Hell never gives salvarsan by intramuscular injection because of the danger of necrosis.

Leir⁸ reports that all patients treated solely with mercury had recurrence.

According to de Aja⁹ neosalvarsan in small doses is beneficial in many cases in which it was once supposed to be contraindicated; for instance, in hereditary syphilis, in nerve syphilis, in aortitis and aneurysm with cardiac compensation and, often, in renal disease. Nevertheless, he concludes neosalvarsan can not safely be prescribed, indiscriminately by every one or for every one.

Wechselmann,⁹ too, says that nephritis is no bar to arsenotherapy, provided only that the kidneys are functionally active. If albuminuria is present, he would advise a primary course of intrafascial injections of neosalvarsan before administering it intravenously.

Schmitt's¹⁰ deductions, drawn from an analysis of von Mentberger's¹¹ book, are that in certain directions arsenotherapy demands care. Patients with circulatory or other grave diseases should be treated cautiously and never in the ambulatorium. The salvarsan solution should be alkaline, as acid solutions predispose to embolism of the lungs. Hepatic complications, even if no more than the passive congestion of heart disease, require especial caution. Too large dosage or too frequently repeated injections may cause fatal renal damage. In the presence of already irritated or crippled kidneys, salvarsan should not be given. The possibility must be remembered that a local Herxheimer reaction may cause a disseminated miliary tuberculosis by its effect on a preexisting, localized focus or produce dangerous symptoms in malignant tumors seated over vital parts. In nerve syphilis salvarsan must be administered early and in repeated,

8. De Aja: *Actas Dermo-Sif.*, 1915, vi, 1.

9. Wechselmann: *Deutsch. med. Wchnschr.*, 1916, xlii, 178.

10. Schmitt: *München. med. Wchnschr.*, 1914, lxi, 1337.

11. Metberger: *Two Hundred and Seventy-Four Deaths from Salvarsan.*

fractional dosage. It must not be used if meningitis exists. Salvarsan and mercury may be used in combination.

On the other hand, Wechselsmann⁹ says that salvarsan and mercury should not be combined, as the result is harmful in at least 50 per cent. of the cases. Fischer,¹² likewise, says that the administration of mercury after preceding salvarsan injections may cause death.

SALVARSAN ACCIDENTS

Simon¹³ says that every active antisyphilitic remedy is liable to excite a serious Herxheimer reaction. Schmitt, already quoted, says that salvarsan accidents are due, in larger part, not to the mercury used in combination, but to toxemias produced by overdosage. A smaller part is to be explained by personal idiosyncrasy. The danger is especially great in nerve syphilis for, unquestionably, neurorecurrences have increased with the use of salvarsan and in spite of every effort to avoid them. Fordyce¹⁴ writes that intensive salvarsan treatment which does not cure tends to promote the development of a state of anaphylaxis and to increase the liability to severe, local manifestations. The late vascular symptoms he attributes to a state of allergy, but questions the theory that nerve syphilis is an anaphylactic phenomenon. He is inclined to believe that it is due to the extension of a primary, meningeal process, seated on the posterior roots between the ganglia and the cord, which causes a degeneration of the afferent fibers and eventually an ascending tract degeneration in the cord. Nicholas and Mutot⁴ found that serious complications, even coma and death, were more frequent after salvarsan therapy, especially if the solution was acid. To the best of their observation, the primary administration of mercury does not lessen liability to salvarsan accidents. Schmitt¹⁰ could find no satisfactory explanation of the part played by salvarsan in the production of fatal metabolic disturbances, or of fatal results in cases of status thymicolymphaticus or of diabetes. He also found no explanation for the large number of cases which develop signs of meningeal irritation, epileptiform attacks or coma after salvarsan. Many alleged salvarsan deaths, Schmidt decided, had no foundation in fact. Fischer¹² would require a necropsy record to be submitted in proof with every claim of death by salvarsan. As regards fatal encephalitis hemorrhagica, in 6,000 necropsies, he rarely encountered a case which could, with justice, be laid at the door of salvarsan.

12. Fischer: *Deutsch. med. Wchnschr.*, 1915, xli, 908.

13. Simon: *Canad. Pract.*, 1914, xxxix, 655.

14. Fordyce: *Am. Jour. Med. Sc.*, 1915, cxlix, 761.

WHY EFFICIENCY VARIES

Takahashi* studied, experimentally, the fate of salvarsan in the tissues. His conclusions were as follows:

1. Salvarsan produces an extensive necrosis of all tissues at the site of its injection. Regurgitation, in animals, occurs, in about 350 days, by a preliminary process of acute inflammation. Fourteen days after the injection, a leukocytic infiltration walls off the injected mass. Gradually the necrotic process is replaced by the granulation tissue of chronic inflammation growing inward from the periphery.

2. The elimination of the injected, insoluble salvarsan has three reactive stages. The primary stage is of necrosis, in which the lymphatics carry away a certain amount. In the succeeding, second stage, the walled-in foreign substance is changed into collections of coarse, opaque globules, which can be dissolved with difficulty. If an abscess forms, some globules are discharged with the pus. In the third stage giant cells invade the remaining mass and take it up. In man such regenerative processes require not less than 400 days.

Stühmer¹⁵ endeavored to trace the injected substances in the tissues by means of a color reaction. Rabbits were used for the experiment. He concluded that neosalvarsan was the most evenly distributed substance and alkaline solutions of salvarsan a close second. Salvarsan, in acid solution, was most abundant in the lung tissue, which seemed to filter it out. Concentrated alkaline solutions were similarly filtered. Concentrated neosalvarsan solutions, on the other hand, distributed the drug uniformly throughout all the tissues of the body. Infiltrations occurred in lung, liver and spleen, rapidly and equally. Storage depots were formed which, in the case of salvarsan, freed small amounts to the bloodstream for three days and, in the case of neosalvarsan, for about twenty-four hours. A large proportion of the salvarsan was eliminated unchanged, by way of the kidneys and the intestinal tract. The latter fact suggested that the symptoms of toxemia might be due to the oxidation of the drug in the intestine, during intestinal disturbances, with resorption of the poisonous product. Stühmer found, also, that repeated injections increased the capacity of the storage depots. Salvarsan seemed to respect the nervous system, but neosalvarsan exhibited a special affinity for the meninges. The result gives a practical hint as to the choice of a remedy in meningeal involvement.

Schümacher† discovered a new test for salvarsan in the urine. During the course of a quantitative, colorimetric urinalysis, he observed that salvarsan answered to all the classic requirements of a true dye. It was absorbed by animal charcoal. It contained (two) aromatic rings, a chromophore (a group of doubly bound atoms, in this instance,

* Takahashi: *Arch. f. Dermat. u. Syph.*, 1914, cxx, 31.

15. Stühmer: *Arch. f. Dermat. u. Syph.*, 1914, cxx, 698.

† Schümacher: *Dermat. Wschr.*, 1914, lix, 1295.

As=As—), and auxochrome groups (which can form salts). Therefore, both physically and chemically salvarsan must be considered a true dye.

The discovery furnishes fresh confirmation of Wassermann's theory that the therapeutic activity of remedies composed of combinations of dye stuffs and poisons is due to the ability of the dye to lead the poison to the diseased cells. This action occurs, however, only when the poison is an essential part of the dye, and not merely an addition to it which can be easily split off. For example, in toluolazo, mercury, silver, salicylic acid, the mercury is not an essential part, but is added to a side chain, so that when the substance is injected into the body, it is easily split off. The dye reaches the diseased cell but the mercury does not. In salvarsan, on the contrary, the arsenic is an essential part of the dye substance and can not be so separated. Consequently it reaches the cell with the dye. Its therapeutic efficiency obviously depends on the ability of its dyestuff guide to penetrate the micro-organisms against which the drug is directed. Those which stain most easily are the most susceptible to the destructive action of the arsenic, to wit, the spirochetes of syphilis, anthrax bacilli, the spirilla of recurrent fever, etc. The organisms which resist the stain are uninfluenced by the arsenic; for instance, the waxy envelope about the bodies of the bacilli of tuberculosis is impermeable to the salvarsan dye. It follows that against tubercular disease salvarsan is powerless.

NEW REMEDIES

Salvarsan natrium is a modification of old salvarsan, which is supposed to be superior to neosalvarsan. It is described by Wechseltmann⁹ as follows: Salvarsan natrium contains 20 per cent. arsenic, the same amount as neosalvarsan. Like the latter, on exposure to the air it changes to a brown color and becomes less soluble and more toxic. It is more soluble than salvarsan and, by so much, easier to use. In eighteen months Wechseltmann encountered but four instances of the so-called anaphylactic reaction, all mild. He found the new remedy safe in all stages of syphilis, with doses of 0.3 gm. to 0.45 gm., and suitable for office administration. Two or three injections, one every week, may be given up to a total of forty or fifty. Recurrences were rare. Eruptions, usually resistant to mercury, yielded to persistent salvarsan natrium therapy. In old syphilis the effect on the Wassermann reaction of the blood and of the cerebrospinal fluid varied from prompt to none. For injection Wechseltmann prefers 1 per cent. dilutions to the more concentrated.

Dreyfus² has used salvarsan natrium with great success in over 450 cases, in from 1 to 1.5 per cent. concentration and in doses rarely exceeding 0.45 gm. Sometimes the drug was used alone, sometimes in

conjunction with mercury. If used alone, it was injected three times a week. If combined with mercury, it was given but twice a week. Over 100 ambulant cases were treated without accident, the patients being required, however, to rest until the morning following the injection. Reactions sometimes occurred, but were never more than slight, transient rises of temperature, diarrhea or attacks of vomiting.

Loeb¹⁶ considers salvarsan natrium as efficient as old salvarsan. His method was to give intravenous injection of salvarsan natrium once a week and intramuscular injections of the mercury salicylate twice a week for a period of four or five weeks.

Pulvis fluens hydrargyri is a mercurial powder proposed by Unna* as a substitute for the less easily prepared and more disagreeable mercurial ointment. It is made by rubbing up metallic mercury with a lycopodium powder, previously soaked in oil of turpentine, in the presence of much air and loosely combined oxygen. The powder which results from the process may be used as such or as an ointment base.

A new method for old remedies was invented by Fischel and Hecht,¹⁷ who obtained intensive mercurial effects by injecting a dose of from 0.015 gm. to 0.04 gm. of mercuric chlorid or of the oxycyanid of mercury (1 to from 200 to 400 c.c. solution) into the cubital vein every three to eight days until eight injections had been given.

SUMMARY OF ARSENOTHERAPY

A few assert that arsenotherapy is efficient without the aid of mercury. This is contradicted by the fact that the search for newer remedies is continued and by the greater prevalence of the combined method. The advocates of arsenotherapy maintain that the method is harmless and is not responsible for the alleged deaths. The opponents answer that, granting the method is falsely accused of death in some cases, the proponents have never produced satisfactory proof of innocence in the remainder; even admitting that the arsenicals merely set a preexisting process in train which causes the death of the patient, the admission of itself proves the method dangerous; and, furthermore, it can not be denied that neurorecurrences have increased with increased arsenotherapy.

Regarding its liability to produce the Herxheimer reaction and the state of anaphylaxis, the debate is about even. Finally, we fail to find in the literature any agreement, even among the advocates of arsenotherapy, as to what constitutes the most efficient dose or concentration. Nicholas and Mutot concluded that while the arsenicals are of unde-

16. Loeb: *Deutsch. med. Wchnschr.*, 1916, lxii, 325.

* Unna: *Dermat. Wchnschr.*, 1915, lx, 337.

17. Fischel and Hecht: *Arch. f. Dermat. u. Syph.*, 1913-1914, cxviii, 813.

niable value they lose in efficiency if not combined with mercury, and that in spite of all dispute, mercury and the iodids still retain their former position and value.

SEROLOGY

Ravaut¹⁸ gives the results of his investigations of the value of the serum test. One result was to convince him that in many quarters too much stress is laid on its evidence. He does not deny any part of its claim to value. He merely deplores the prevailing tendency to regard the test reaction as a mathematical certainty, when the facts justify nothing of the sort. The test, admittedly, possesses many sources of error. Ravaut's experiments bring some into strong prominence. Assuming for the purpose of the argument that the serum test is infallible, Ravaut turned his attention to the personal element in the interpretation, to the influence which personality exerts. Three identical samples were sent to three different serologists and the interpretations of the test reactions compared. He found that 61 per cent. agreed, 36 per cent. varied from positive to doubtful or negative, and 3 per cent. differed absolutely. It was noticeable that the reports conflicted less in tests of avowed syphilitics than of nonsyphilitics.

Ravaut challenges the claim of invariable accuracy for the Wassermann test. He has seen positive reactions persist for years in numbers of instances, despite most vigorous treatment and although no other symptom ever developed. On the other hand, he has seen cases of ocular, cutaneous or visceral disease, unquestionably syphilitic, in which the reaction was invariably negative. Ravaut also claims that there are various conditions which may create a false positive reaction in nonsyphilitic serums, as, for example, injections of autoserum. Of fourteen nonsyphilitics, previously negative, after experimental injections of arsenobenzol 35 per cent. gave positive reactions. Ravaut freely admits that a positive Wassermann test usually means active syphilis and that a negative test does not prove the contrary; but he claims that, while it is desirable to convert a positive reaction into a negative by treatment, it is sometimes impossible. In such cases Ravaut ignores the test and bases his prognosis on other clinical factors. He believes that not even a positive Wassermann reaction can always be accepted if it is not confirmed by other symptoms or evidence.

Keyes¹⁹ insists that the diagnosis of syphilis should not be made on the sole evidence of a Wassermann test. He argues that such methods are illogical. The test is admittedly nonspecific; its results depend too

18. Ravaut: Errors in the Interpretation of the Wassermann Reaction, *Ann. de dermat. et de syph.*, 1914, Series 5, v, 285.

19. Keyes, E. L.: Some Clinical Features of the Wassermann Reaction, *Jour. Am. Med. Assn.*, 1915, lxiv, 804.

much on the technic and too often manifest utterly inexplicable vagaries. Although all agree that a negative test does not disprove the existence of active disease and, much less, that it assures future immunity, a number of alleged cases of reinfection have been reported whose sole foundation was a former negative Wassermann.

Weisenburg²⁰ says that the Wassermann reaction cannot be made to dominate the diagnosis, even though its great value can be granted without reserve. As a matter of fact, the serum reaction is only a single symptom. Its presence or its absence is a no more indispensable factor in the clinical diagnosis than is any other single symptom. The serum test method has not yet shown why we should discard the ancient dictum that one symptom does not constitute a diagnosis.

Fruhwald²¹ has demonstrated by animal experimentation that the blood of syphilitics may contain and may transmit to animals the virus of syphilis, although its serum reaction is consistently negative.

Heimann²² accepts the evidence of the positive Wassermann test if it can be shown that it has not been influenced by certain nonsyphilitic states which, notoriously, tend to falsify the reaction. On the other hand, the negative test is so regularly in error during certain stages of syphilis and in the presence of many other extraneous factors that it can never be accepted without reserve.

Uhle and Mackenney²³ tested the reliability of the Wassermann reaction from the clinician's standpoint. Seven different serologists, employing different methods, were selected to test the 325 specimens from 292 persons. In every instance identical serums were sent to at least three of the seven operators. The reports were then compared. From 2.5 to 18.1 per cent. of normal and nonsyphilitic persons were reported positive, the percentages varying with the operator. The percentage of positive reports ranged, according to the test method, from 50 to 100 per cent. Five of the seven serologists agreed in 47 per cent. of their total results. It was noteworthy that the serologists who most consistently reported positive tests which clinical expectancy confirmed also most consistently returned doubtful or negative reports when the clinical evidence was doubtful or negative. In 21 per cent. of the total reports there was full agreement; 10 per cent. disagreed completely, and in 61 per cent. of the total reports not more than four conflicted in any one case. The specific antigens gave the smallest number of

20. Weisenburg, T. H.: The Value of the Wassermann Reaction, *Jour. Am. Med. Assn.*, 1915, lxiv, 975.

21. Frühwald: *Derm. Wchnschr.*, 1914, lix, 863.

22. Heimann, W. J.: The Wassermann Reaction as a Clinical Test, with Special Reference to Its Bearing on Matrimony, *Jour. Am. Med. Assn.*, 1915, lxiv, 1463.

23. Uhle, A. A., and Mackinney, W. H.: Comparative Results of the Wassermann Test, *Jour. Am. Med. Assn.*, 1915, lxv, 863.

positive tests, except in two cases. On the other hand, their reactions were most often confirmed by the clinical evidence. It seemed to make no difference in the accuracy of the reaction whether the specimen was collected in sterile or unsterile containers, whether or not the blood was contaminated by virulent strains of the typhoid bacillus, of the *Staphylococcus pyogenes-aureus* or of the streptococcus; whether the specimen was one or several days old; or whether the blood was drawn when the stomach was full or when it was empty. So far as a few cases could show, acidosis did not seem to influence the reaction.

Glomset²⁴ accepts the unsupported evidence of the serum test without hesitation.

Kolmer and Schamberg²⁵ conclude that the Wassermann method is not sensitive enough. They often obtained a positive result with cholesterinized serums when, by the Wassermann method, they got a negative. They believe that the sensitized serums furnish reliable proof of the presence of active disease. Nevertheless, they advise that the results should be analyzed in the light of the history and of the clinical signs. Confirming their claim of its greater delicacy, the cholesterin reaction was less easily converted to negative by treatment than the Wassermann.

Hell⁷ questions the absolute accuracy of the Wassermann test in its prognosis of congenital syphilis. He found it difficult to change the positive reaction of congenital syphilis to negative even by energetic treatment. He inferred that in congenital cases a positive Wassermann test may not invariably indicate active disease.

CUTANEOUS TESTS AND OTHERS

Noguchi's cutaneous luetin test has been well received in this country, though not abroad. Sherrick²⁶ reports that both syphilitic and nonsyphilitic cases gave positive cutaneous reactions to luetin inoculation if potassium iodid or any other iodine-containing substance had not been administered just before, at the same time or shortly after the performance of the test.

Klausner²⁷ includes in his article an interesting review of the general subject of cutaneous tests. Pallidin is a substance obtained by Fischer's method of making extracts from lung tissue.²⁸ Klausner's

24. Glomset, D. J.: Congenital Syphilis in the Light of the Wassermann Reaction, Jour. Am. Med. Assn., 1915, lxxv, 682.

25. Kolmer and Schamberg: Am. Jour. Med. Sc., 1915, cxlix, 365.

26. Sherrick, J. W.: The Effect of Potassium Iodid on the Luetin Reaction, Jour. Am. Med. Assn., 1915, lxxv, 404.

27. Klausner: Pallidin Cutaneous Test, Arch. f. Dermat. u. Syph., 1914, cxx, 444.

28. Equal parts of the saline and of tissue, by weight, ground up with glass, centrifugalized, heated to 60 F. for twenty-five minutes, and phenol (carbolic acid) added to make 0.5 per cent.

estimate of its value is as follows: 1. In syphilis, preparations made from tissue rich in spirochetes by a similar technic also give positive cutaneous reactions. 2. A positive reaction is a local, inflammatory infiltration, which reaches its height in thirty-six to forty-eight hours after the inoculation. 3. The pallidin test is specific for syphilis, and especially for the tertiary and late hereditary forms. 4. In precocious, malignant syphilis the reaction is often positive or negative in correspondence to the Wassermann reaction. 5. Visceral gummas are positive to the pallidin test. 6. In cases of parenchymatous keratitis the pallidin test is more often positive than the Wassermann. 7. Gummas of the periosteum and cachexia are often negative to pallidin. 8. Tertiary syphilis and the late, hereditary disease yield a higher percentage of positive reactions to pallidin than to the Wassermann test. Treatment does not greatly influence the pallidin reaction, although if intensive it does sometimes cause it to disappear. Pallidin may excite a positive allergic reaction where previously the serum reaction was negative. The reaction to pallidin is to be interpreted as a phenomenon of anaphylaxis.

Fränkel and Thiele²⁹ investigated the coagulation test for syphilis, proposed by Hirschfeld and Klinger. Nonsyphilitic serum was found to coagulate within fifteen minutes, the time varying with the method employed. Syphilitic serum exhibited a delayed coagulation. The coagulation test, which depends on fixation of the complement, appeared to correspond in most instances to the Wassermann test. Brant³⁰ drew similar conclusions from his experience with 500 tests. He reports that as a rule the results of the coagulation method and of the Wassermann agreed. When they differed, the history and the clinical signs favored the coagulation test.

Pfeiler and Scheyer³¹ recommended the employment of hemolysin and hemagglutinin as indicators of complement fixation in syphilis and as a parallel method to the Wassermann. They reported several cases of suspected syphilis in which these methods were positive when the Wassermann was negative.

CILIA A DISTINGUISHING MARK OF TREPONEMA

Fontana³² reports a new method of staining by means of which he succeeded in demonstrating that the treponema possess cilia. He estimates that the length varies from one to seven times that of the windings of the organism; that the cilia occur in both straight and spiral forms; that they may be at one or at both ends of the organism;

29. Fränkel and Thiele: München. med. Wchnschr., 1914, lxi, 2095.

30. Brant: Deutsch. med. Wchnschr., 1915, xli, 915.

31. Pfeiler and Scheyer: München. med. Wchnschr., 1915, lxii, 393.

32. Fontana: Derm. Wchnschr., 1914, lix, 1367.

that they are exceedingly thin; and that, though they stain weakly, they nevertheless stain sufficiently to be photographed. Most specimens of cilia do not end in a point but in a more or less well-developed, club-shaped swelling, three or four times as thick as the cilia itself, which stained moderately well. This last observation Fontana considers unique.

MANIFESTATIONS OF CONGENITAL SYPHILIS

De Aja³³ believes that congenital syphilis is in reality extraordinarily frequent. His cases varied in age from 8 to 53. Examples of the so-called late or adult syphilis were not rare. Usually the history in such cases revealed the existence of syphilis in the parents. Their own most frequent symptom of the inherited infection was disease of the long bones. De Aja believes that these cases of late manifestations of inherited syphilis are frequently unrecognized, because the observer fails to take into account every factor connected with the lesions, the symptoms and the history and because he does not comprehend how frequent inherited syphilis really is or how it may make itself manifest.

In their discussion of the manifestations and the diagnosis of congenital syphilis Soldin and Lesser³⁴ manifest that comfortable reliance on the unvarying truth of the Wassermann reaction which Ravaut so deplored. The writers examined a large number of infants and children who were admitted to the hospital for nonsyphilitic diseases and who, therefore, showed none of the ordinary signs of syphilitic inheritance. In such cases snuffles were never pronounced, skin rashes were few, and epitrochlear glands were barely palpable. Enlargements of the spleen or liver were the most important symptoms of their syphilitic inheritance. Many children showed not the slightest sign of syphilis, not even a positive serum reaction. Nevertheless, Soldin and Lesser unhesitatingly proclaimed them syphilitic because their mothers invariably yielded positive tests. They concluded that in children, even when corroborative evidence fails, bare suspicion is sufficient reason for testing the mother's blood. If the result is positive, the child must be regarded as a victim of inherited syphilis.

Haberman³⁵ calls attention to the fact that although syphilis may be one of the great inherited causes of degeneracy, it is not the sole cause. Therefore, to avoid harmful error, the possibility of a non-syphilitic origin can never be ignored.

Vignoli-Lutati³⁶ maintains that many cases in which the enlarged cervical glands break down and produce scars are wrongly attributed

33. De Aja: *Actas Dermo-Sif.*, 1914, vi, 193.

34. Soldin and Lesser: *Deutsch. med. Wchnschr.*, 1915, xli, 429.

35. Haberman, J. V.: *Hereditary Syphilis*, *Jour. Am. Med. Assn.*, 1915, lxiv, 1141.

36. Vignoli-Lutati: *Arch. f. Dermat. u. Syph.*, 1914, cxx, 376.

to tuberculosis. Yet no proof of tuberculosis has ever been demonstrated. Because of their occurrence in association with congenital syphilis, because tuberculosis has not been proved and because the symptoms respond promptly to antisiphilitic treatment, Vignoli-Lutai is convinced that the true cause is not tuberculosis but inherited syphilis.

TRANSMISSION OF SYPHILIS

Glomset²⁴ is of the opinion that the syphilitic virus may be transmitted to the fetus by way of the placenta and that the infection usually occurs late in gestation.

Fordyce¹⁴ states that the manner of fetal infection is indirect, that is, through the mother; that the later the stage of the disease in the mother, the greater chance that the fetus will escape; and that he believes that the spirochetes pass from the mother through the placenta to the blood of the child.

As has just been noted, Soldin and Lesser maintain that even though the offspring show no visible signs and even though they manifest negative Wassermann reactions, the positive serum tests of their mothers is sufficient to prove that the children are syphilitic. The lack of evidence in the children, they say, is due to immunization during intrauterine life, with a consequent prevention or hindrance to the further development of spirochetes in the offspring.

Trinchese³⁷ has collected data concerning congenital syphilis from various sources, which he interprets as follows:

1. It is impossible for the fetus to immunize the mother (Colles' law). Paternal infection of the fetus, alone, does not exist. Moreover the fetus has never been shown to possess immunizing substances.
2. The immunization of the fetus by the mother (Profeta's law) is not an infallible occurrence.
3. The earlier the infection of the fetus, the more rapid the development of a septic syphilitic process which is fatal within six months.
4. The mother may have a positive Wassermann and the fetal tissues may abound in spirochetes, and yet the fetal reaction will be negative, because the fetus builds no reaction substance until about its eighth month. After the eighth month the fetal blood for the first time begins to respond positively.
5. If infection occurs in the last weeks of gestation, the infant may possess neither clinical symptoms nor a positive serum reaction, because the time permitted the spirochetes for incubation has been too short. Such cases were once considered immune. In fact they are the cases in which the late manifestations of inherited disease develop.
6. If the mother is syphilitic, neither the absence of clinical signs nor of a positive serum reaction is

37. Trinchese: *Deutsch. med. Wchnschr.*, 1915, xli, 555.

positive proof of health. 7. Four possible eventualities confront the offspring of syphilitic mothers, which in the order of their gravity are clinical freedom and a negative test; clinical freedom and a positive test; clinical signs and a negative test; clinical signs and a positive test. The last is inevitably fatal.

We have considered above the possibility of transmission only by the mother with a positive Wassermann reaction. Frühwald's³⁸ experimental inoculation of a syphilitic rabbit's testicle indicates that the blood of a syphilitic mother, without either visible signs or a positive Wassermann reaction, may, nevertheless, be infectious.

The advent of the Wassermann test has not caused Keyes¹⁹ to alter his views concerning the marriage of syphilitics. He can see no reason for changing the old rules.

Heimann²² will not consent to the marriage of syphilitics so long as the serum reacts positively; so long as a sufficient period has not elapsed, without symptoms, after disappearance of the positive reaction under adequate treatment; or so long as the serum gives a positive response to provocative injections of salvarsan.

Nicholas and Mutot⁴ recommend the retention of the old rules concerning syphilitic marriages.

SUMMARY

Three broad conclusions may be drawn from this exposition of the literature on the subject of syphilis:

1. Today all parties concede the right of the arsenicals to a place in the sun of syphilitic therapeutics. Nor does the concession invalidate the claim that mercury and the iodids have lost nothing of their original worth (Nicholas and Mutot).

2. The Wassermann and the other serum tests are seated more firmly in their original position as efficient aids to diagnosis, but have failed signally to deprive clinical methods of their old importance.

3. In short, the newer methods of diagnosis and of treatment have strengthened our hands immeasurably. The older methods have held their own. Combined, they mark a noteworthy advance in the subject of syphilis which neither could accomplish alone.

38. Frühwald: *Dermat. Wchnschr.*, 1915, 1x, 513.

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THE NEUROTIC CHILD

SOME FAMILIAR SYMPTOMS AND THEIR PROBLEMS *

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The intensive work done during the last twenty years on the functional nervous disorders of the adult has brought about a marked change of attitude in dealing with them. We are less inclined to attribute these disorders to hypothetical intoxications, nor are we satisfied with a mere reference to the basis of constitutional psychopathic inferiority on which they arise; the aim is now to find the meaning of each disorder, the rôle that it plays in the adaptation of the individual to the environment. We look on fever not as a disease, but as part of a mechanism of adaptation; so in a functional nervous disorder, whether it be a paralysis or blindness, morbid fears or obsessive thoughts or compulsive acts, we see adaptation to the complex environment, an adaptation which is inferior and unhygienic, but intelligible and often open to modification.

In studying these disorders, whether they belong to hysteria, the anxiety neuroses, the compulsion neuroses, or to less clearly defined neurasthenic and psychasthenic groups, one is compelled to go beyond the usual impersonal categories of internal medicine and to study the organized driving forces which are at the basis of human behavior. We are wont to assume that our judgments are the result of purely rational processes, that our actions are determined by purposes more or less clearly realized; we support our emotional prejudices by logical reasons, explain our preposterous behavior by the introduction of worthy motives, and in these reasons and motives our official personality finds much comfort. The unembarrassed study of the real biologic unit takes us beneath the surface to other dynamic factors, to more elemental and deeply rooted forces which drive us, but which we are used to ignore; we find that beneath the civilized surface the savage still survives, and the child may continue to direct the activity of the apparently emancipated adult.

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Neurotic symptoms to a large extent find their explanation in these underlying trends and among the determining factors of the symptoms a prominent place must be given to the attitudes, the problems and the conflicts of childhood. The psychopathologist is bound to have a keen interest in the problems of adaptation or behavior in childhood; he must observe the early indications of difficult adaptation, he must study the various types and early stages of unhygienic adaptation. The child, too, may then be found to have an unsuspected complexity of forces determining his behavior; here, too, the real biologic unit may be different from the conventional presentation, much more complicated than the cherub of the painter and the poet, or than the delightfully simple individuals who are supposed to inhabit our nurseries.

The recognition of this complexity may enable us to understand some of the nervous manifestations of childhood, which otherwise would be unintelligible. In this way the study of the adult and that of the child reinforce each other; beneath the adult reactions we can trace problems of the child, while the child's life at an early age may show indications of conflicts which tradition only admits in the adult. The psychopathologist, from his studies of the adult, is in a position to indicate to the pediatricist factors in the child which are apt to escape his notice, while the pediatricist has the opportunity of observing directly the reactions of the child and collecting material which will be of the greatest value to the psychopathologist.

A familiar situation may be chosen to illustrate the persistence of a childhood trend in adult life. The man of somewhat exaggerated independence, rather defiant toward teachers, heterodox in religion, very radical in politics, is inclined to explain his views as based on grounds of pure reason; but his general attitude of protest against authority may be merely the persistence of his old childhood conflict with the main authority of that period, the father. All trace of the original inarticulate feeling of protest may have been lost from consciousness, and yet it may survive and exert its influence beneath the conscious filial devotion of the adult. One does not have to look far to see examples of perplexing estrangement between father and son, mother and daughter; the antagonism is apt to be referred to some comparatively recent situation, and those concerned fail to see the childhood roots of the difficulty. It may, however, not be estrangement, but the reverse, that strikes us; there may be an excessive devotion and this may be the individual's defense against the latent disloyalty, as if the poor heir to a millionaire were to be morbidly worried about the trifling indisposition of the latter. Love and subconscious hate may be strangely blended and the devotion of the daughter to a mother, whose selfishness has dwarfed the girl's life, may draw its strength from both sources.

A girl marries an elderly and unsuitable husband to the bewilderment of her friends, who fail to appreciate at its true dynamic value the likeness of her husband, even in his faults, to the father, the object of her early devotion, and still the pattern by which unconsciously the emotional value to her of other men is determined.

These early affections may persist unmodified and direct the behavior of the adult to such a degree that we are entitled to look on this persistence as a neurotic symptom; it is an indication of the inability of the individual to pass from one phase of development to another, an evidence of want of emotional flexibility or maturity, a neurotic conservatism.

The persistence of this earlier attitude conflicts with the actual demands of the adult life; the man who unawares continues into his married life the affectionate attitude of the dependent child may be unable to account for strange difficulties of adaptation to married life, which find an expression in psychoneurotic symptoms.

This was the case in a married man of over 40, who was subject to periodic alcoholism, which masked recurrent moods of depression. An analysis of his case revealed the intimate relationship of these symptoms to the want of maturity of his emotional life, which had hampered his adjustment to married life. A cultured and apparently independent adult, he had much of the affectionate dependence of the child; although babified and protected from annoyances by his wife, he was not completely satisfied with her devotion, he grudged the love she gave her children, he seemed to crave some affection which he could not find, and at times in his moods of childlike desolation and helplessness he indulged in alcohol to excess. The basis for his unsatisfied longings seemed to be the persistence in his emotional life of the attitude of the child. From the age of 11 to 22 he had slept in the room of his widowed mother in order to attend to her invalid wants. When he was 22 an aunt said that she was going to wean him from his mother, and gave them rooms which were far apart. He became sleepless and lonesome, and it was to meet the sleeplessness which followed on this separation from his mother that his alcoholic indulgence owed its beginning.

The close relationship between his sleeplessness and his dependence on his mother was illustrated by an earlier episode. At the age of 17, on the death of his sister, he was sleepless for about a month; bromid failed to induce sleep; "the only way I could get sleep was to get into bed with my mother—it seemed to soothe me."

This neurotic exaggeration and persistence of the normal emotional dependence of the child on the mother could not be altogether laid at the door of unknown constitutional factors; it was no doubt fostered by the injudicious training given by the overaffectionate mother to her

only son. The mother probably did not realize that she might cultivate in her child a degree of emotional dependence which would be the dominant factor in his adult life and seriously interfere with his mature development. The patient himself had not realized the presence in his adult life of these driving forces, and derived immediate benefit from being put in a position to face clearly the actual factors underlying his difficulties in life.

The sleeplessness of this patient deserves attention; the comfort of the mother's presence responded to deep-seated cravings of his emotional life, which if left unsatisfied meant sleeplessness. In this case the situation was clear, and it is worth while keeping in mind the general principle that the sleeplessness of the neurotic adult may be due to obscure emotional cravings. The sleeplessness of the neurotic child, when separated from the mother's bed or room, may well be of similar origin; the temptation to resume the old sleeping arrangements may be great, but one must remember that the transition has to be made sometime and it is better to make it early than wait until habit has strengthened the emotional dependence.

The disproportionate or neurotic attachment for one parent may involve a converse antagonism to the other parent, it may be at the basis of jealousy of brother or sister, and these factors may express themselves indirectly in neurotic symptoms.

These facts may be granted to throw light on the neurotic disorders of the adult, but may seem of little application to the supposedly simple life of the child.

Before passing to the discussion of some cases which suggest that the same mechanisms are present in the child as in the adult, reference may be made to some other symptoms in the adult, as we shall meet similar symptoms in the case of the children.

A married woman of 32, never in love with her husband, with rather poor habits and standards, for some years had a rather intense sentimental relationship with a married man. About this time she began to show a quite exaggerated degree of personal cleanliness, washing her hands incessantly; the absurd but imperative cleanliness was the compensation for and indirect recognition of the underlying impurity which the patient did not care to face. The patient herself showed some insight into the mechanism of her disorder when she said, by way of spontaneous criticism of her symptoms, "It is better to have a clean soul than clean hands."

A similar explanation for the nervousness was found in the following case:

A schoolgirl of 16 began to fret about not being perfect in her school work, she read things over and over for fear she had not read them quite correctly; she wrote and rewrote letters; she showed a scrupulous worry about whether she had done her duty in asking her parents questions about her school plans.

This girl, with the obsessive striving for perfection in her less personal activities, had, as a matter of fact, been secretly living in a dissolute way for some time.

In the adult and the adolescent exaggerated standards frequently indicate the reaction of the personality to an underlying feeling of guilt, or discomfort, or inferiority; it is important to note that it is a reaction to this "feeling," not to the clearly recognized admission of these factors. There may be no clear recognition of them; consciousness may contain no direct trace of them; in fact the obsessive symptoms help to keep these intolerable elements from invading consciousness.

Such obsessive striving is not, however, limited to the adult and the adolescent; we find the same symptoms at an even earlier age.

A. G., a girl of 12, was brought to the dispensary of the Phipps Psychiatric Clinic Aug. 31, 1914.

The patient, a rather frail child, with some evidence of pulmonary tuberculosis, complained of many nervous symptoms. Her sleep was disturbed, and she had frequent night-terrors; she had distressing dreams of snakes and other animals, of the family being murdered, of her sister cutting her in pieces and sealing her up in cans. Even when awake at night she heard imaginary noises, such as bells ringing; she appeared also in her waking state to see animals chasing her. The mother suggested that these experiences might at least in part be misinterpretations of actual sounds.

During the following months the patient showed little improvement, the night-terrors and bad dreams persisted; on one occasion she talked of seeing snakes on the wall, and showed evidence of some suspicion, accusing her sister and mother of having talked about her.

In November the nervous symptoms were gone into more carefully. In sleep the patient tossed and tumbled in bed, but for some time had been free from bad dreams. If she read disturbing incidents in the paper, she slept worse at night. The mother, finding that she had to rise every night to quiet the patient, ended by taking the patient into her own bed and sleeping with her in her arms.

As to her morbid fears and scruples, she scrutinized every drop of water or milk to see that it was absolutely clean; she was afraid to eat if her hands had touched anything, and therefore was taking insufficient nourishment; she washed her hands constantly. In bed she worried over the possibility of having eaten anything without washing her hands; she was tormented by thoughts of having done something that might harm her, as, for example, "I think I swallowed a fly, will that hurt me?" She expressed fears of death, wondered if she had eaten enough to keep her alive till the morning. She fretted over minor acts of disobedience during the past day, and kept harping on them in distress "until the perspiration rolled off her." Every night she looked under the bed, fearing somebody might be there.

The patient was abnormally timid, hesitated to pick up a chicken for fear it might peck her. She was prudish and would not undress or bathe in the presence of her sister or mother. At the same time her timidity would not allow her to go to the outdoor toilet without her sister or mother coming in with her. Although at night she fretted over her disobedience and promised to amend her ways, in the daytime she was not very obedient, evaded all distasteful work, and the mother gave in to her "just to have peace."

During the following two months the patient on the whole slept somewhat better. She was now sleeping with her sister, but occasionally at night she

was scared and would call for her mother, wanting the latter to take her into her own bed. She still asked frequently if she were going to die, and at night asked if she would be well in the morning.

In January, 1915, the symptoms showed little change; at night, in bed with her mother, she spent over an hour asking incessantly whether she would be all right, whether she would die, whether anyone else of the family would fall sick. She discussed whether she had been sufficiently virtuous during the daytime, as, for example, "have I obeyed the doctor's orders and gone out enough today?"

In the daytime she was inseparable from her mother, would not go from one room to another without her. At her bath she insisted on being alone, but requested her mother to be in the adjoining room so that she could talk to her. She still scrutinized her food and drink very carefully, removed from her cereal any particle that was too brown; she washed her hands an unnecessary number of times.

During 1915 the patient made some improvement. Jan. 8, 1916, she was less timid and less prudish, did not cling so closely to her mother, in fact had on one occasion spent a whole afternoon with a friend away from her mother; previously she would not have thought of going anywhere without her mother. She now indulged in no unnecessary washing of hands, scrutinized her food less, and for some months had not asked if she was going to die. She still worried in an obsessive way about possible lapses, and at night repeated such questions as, "Am I a good girl?" The patient is now almost 14 years old and has not menstruated.

Can the obsessive cleanliness of this child, her exaggerated scruples as to her behavior, receive the same explanation as the same symptoms in the preceding cases? In that case we should assume an underlying feeling of discomfort with regard to personal factors, which the patient had not learned to face in a straightforward way. In the previous cases the personal conflict which was at the basis of the nervousness was in relation to the instinctive life, and it is possible that in the present case the same factors are at work, for the instinctive difficulties of the adult have their analogue in the life of the child. The patient was an extremely quiet and uncommunicative girl whose inner life it was not possible to fathom. In the treatment of such a case it is well to keep in mind the possibility that there are important trends beneath the surface, which do not express themselves directly; that these trends may have undue emotional value as a result of the influence of the environment; that the nervous symptoms may be merely a substitution or compensation for these subconscious factors. With this possibility in mind, the physician may do something to help the child toward a more healthy and open assimilation of factors, which to the child have presented an insoluble problem.

That we are not reading into the child's life a complexity of structure which only exists in the adult will be seen by some other cases, in which the underlying factors could be elicited. The problems presented by this girl of 12 have also cropped up in her cousin, a woman of 25.

The patient for more than a year had suffered from a morbid fear of contamination; this had developed after a bottle of douche medicine had been broken. The patient came to feel that everything might be contaminated, that she might carry the contamination to others; she was afraid to eat, for fear the dishes might not be clean; she slept for weeks on the couch for fear the bed might be contaminated; she sometimes spent eight hours out of the twenty-four in her ablutions. Out of her complete clinical history only one group of symptoms will be referred to, namely, those relating to her mother; these symptoms had made their first appearance at the age of 5 or 6. At that age, when she first went to school, she was accustomed to go half a block and then go back to ask her mother if she felt all right, if she felt she would die before the patient returned from school, if she were pleased, if she thought anything would happen, etc.; she sometimes repeated this performance two or three times before she arrived at the school.

In view of these symptoms we might be inclined to postulate merely a rather exaggerated emotional dependence of the child on her mother. The possibility of another interpretation is brought up by the following facts: This girl, with the great solicitude for her mother's welfare, from the age of 16 had tantrums in which she bit and scratched her mother, and called her "fool" and "devil." She had of recent years asked her mother somewhat perplexing questions, as, for example, "Mamma, do I wish you were dead? Would I rather have someone else for my mamma? Would I rather have you dead or living? Mamma, I don't mean that, do I? Is it just a bad thought?" The patient thought sometimes it was the devil that made her think those things.

Even before the age of 6 (the patient's statement) she often asked her mother if she were her mother's own child, or if she were an adopted child. Where do these elements come from that seem to contrast so strikingly with her official devotion to her mother? Must we assume that it is the devil at work, playing the same pranks he loves to play on conscientious ministers, who begin to find strange oaths and blasphemous remarks rising to their lips with obsessive force? In such cases a frank examination often shows that the life-long religious earnestness of the patient has developed partly as a defense against the recognition of elemental forces, which the individual obscurely feels can not be dealt with in the way that other human problems are met. So the neurotic devotion to the mother in the present case may be a defense against the recognition of a latent antagonism, which the personality feels itself unable to deal with. Such an antagonism may seem to some to be a rather rare perversion of the normal emotional life; on the contrary it is an inevitable result of the situation. The child seeks to assert itself, to dominate the environment, to live out its own natural trends, and in adapting itself to the necessary restrictions of an ethical environment it inevitably feels a restriction of its personality, and has some antagonism to the restricting forces. It is largely through the mother that the cultural environment brings its restrictions to bear on the child. So beneath the instinctive dependence and love of the child it is natural that we should find certain feelings of restriction and antagonism; and in the neurotic child both the oppos-

ing forces may have unusual strength, with symptoms such as those of the present case.

It may seem rather revolutionary to allow to a child of tender years an emotional life of such complexity, and it may appear especially difficult to accept such views in relation to the attitude of the child to the mother, where convention demands a unitary attitude of love.

The same peculiar blend of love and antagonism will perhaps be more readily admitted where we are dealing with a brother or sister, as in the following cases:

J. F., a boy of 7, was referred to the dispensary of the Phipps Psychiatric Clinic from the Harriet Lane Home, March 20, 1914. Following an attack of chickenpox in January he had shown peculiar nervous symptoms; previously of nice disposition, he was now rather irritable and sensitive; he did not want people to look at him and talk about him. Four days after recovery from the chickenpox he began to express odd ideas; he said that his feet were growing large and that his hands and nose and mouth were also increasing in size. After some time he ceased to express such ideas, but began to dream of snakes; he was now afraid to go into rooms alone, and one day when sent upstairs he was found shaking and crying, and claimed that he had seen a big black snake coming after him. He also dreamed of robbers. Some of his ideas seemed to depend partly on rather simple occurrences; thus, his fear that his nose was growing large may have been partly determined by the fact that his mother, when he had frequent nosebleed, had warned him not to touch his nose or it would get big. Other symptoms seemed to have a rather deeper origin. The boy dreamed of robbers, but in the dreams the robbers killed his little brother B., and cut him up in pieces; he also dreamed that B. was drowned. The mother stated that the patient was very fond of B., but she remembered that when B. was a little baby, and nursing, the patient, 5 years of age at the time, used to try to push B. away from her. The patient himself, in discussing B. with the physician, showed clear evidence of some jealousy; he said, "B. is the pet and sits in mother's lap; he is the pet because he always sleeps next to mother." The patient's jealousy of his little brother may also have been at the root of the feeling that he had been growing quite small, "like B."

In the robber dreams, in which his brother was removed, and in the dreams of B.'s death by drowning we see accomplished something which no doubt corresponded to the obscure longing of the boy, the removal of his rival in his mother's affection. Through the disguise of the dream one could see some of the important emotional factors in the boy's life. The symptoms had developed after the chickenpox and might be considered as in some vague way the expression of physical reduction; but the chickenpox had not only caused a fever, it had created a new situation. Before the chickenpox the mother and the children had slept in the same bed; on the onset of the chickenpox he was left alone in the bed, while his mother and little brother slept on the couch. It is therefore intelligible that the latent feeling of rivalry should be rendered keener by this new situation, and the dream may well have been the expression of those trends, which in the daytime were not allowed to express themselves directly.

Whatever the mechanism of the dreams, they at least guide us to important forces which otherwise might escape detection. They enable us to realize something of the complexity of the child's nature, to see beneath the simple and naïve surface repressed factors of great personal significance. Already at the age of 7, in his reaction to a trying emotional situation, we see that the child, in accepting that restriction of his emotional demands, which is involved in the equal demands of others, has difficulty; he develops peculiar reactions, which in a way give expression to the repressed trends.

For the treatment of such a case it is important to recognize the real factors involved and not to be satisfied with vague hypotheses as to toxic processes or with references to constitutional instability. It is true that such a reaction indicates that in face of a sufficiently banal situation the individual has not shown the normal degree of adaptability; the situation has been a test of the constitutional nervous stability of the individual. While this is true and while the constitutional limitations have to be recognized, the true nature of the test must not be overlooked, the possibility of making it less severe must be considered, and the way discussed in which the child with his constitutional lack of resistance may be trained to develop these special qualities, which are of importance in meeting personal problems. In that case the reference to a constitutional basis will not mean a fatalistic attitude, but will be followed by a keener sensitiveness to the problems of the child and a more enlightened way of dealing with them.

Here again light is thrown on normal psychology by the study of the reactions of the neurotic individual; the above case illustrates in a clear and dramatic way the presence of certain factors in the life of the normal child, which otherwise might escape us. The evidences of jealousy shown by normal children are often overlooked or are treated as rather amusing and negligible factors; yet they are quite serious factors in the life of the child. The normal child, who asks the mother to throw the baby out of the window, is prompted by the same forces which, in the child mentioned above with less favorable nervous balance, led to disturbing dreams of disaster to the brother.

A case illustrating the presence of the same forces at a still earlier age was that of T. A., the delicate son of a nervous mother. When he was 19 months old a baby brother was born; the patient appeared to be rather upset by this event; he was in bed for three days, and the physician thought he was jealous of the newcomer, "heart sick." "He didn't seem to want to walk," and for some time he required to be carried or taken in the go-cart; it was as if he demanded the attention which was given to the baby. His mood seemed to change, he was a little "distant" with his parents.

On several later occasions he showed evidence of the same trends; he wished that the baby were not there, he said that his mother did not love him, "you won't see me any more," "the dear God loves me."

In the third year of his life he had three "spells;" the first was elicited by his mother slapping him for obstinacy in refusing to lie down; the child held

his breath, became blue in the face. The second spell came on when, after clamoring insistently for something, he was scolded by his mother; he held his breath, became blue, appeared to lose consciousness. The third spell came on after he had been struck by his little brother. The child died in his fourth year from pellagra.

Here again there may be some reluctance to see in a child of these years evidence of complex factors which we are rather apt to consider of importance only at a more mature period. It is true that it is only at a later period that they come clearly into consciousness, and are apt to form clearly recognized motives. But it needs little maturity of intelligence to have a craving for affection, to be self-assertive, to demand affection of an exclusive nature; a child can feel in a very subtle manner, its intuitions are keen, and we have to remember that our life is determined not so much by intelligence as by those driving forces deeply rooted in the instinctive life of the individual.

If one wish further illustration of the deep, underlying forces that sway the child's emotions, influence its reactions and are at the basis of many neurotic symptoms, there is available an extremely interesting presentation by Jung¹ of the conflicting forces in the nature of a girl of 4. The birth of a brother at that age proved to be a rather unsettling factor; the announcement of the probable arrival of the brother had already elicited the prompt answer, "then I would kill him." The problem introduced by this new factor into the situation of the child apparently led directly to the development of unusual moods, night terrors, ruminations, and some estrangement from the parents.

The fact that a child of 4 should have so much difficulty in assimilating a situation which many other children deal with in a very placid manner in itself gives one a measure of the nervous sensitiveness of the child. It is interesting, however, to note that before this very specific test was applied the child, who, it is true, was rather imaginative, had shown no evidence of nervous instability.

In paying so much attention to one factor in the life of the child, a factor it is true of cardinal importance, the aim has been to illustrate in some detail the important principle that neurotic symptoms may be the surface expression of complicated conflicts in the child's personality. No attempt has been made to sketch in all the main outlines of the child's life. There are many other problems before the child than those referred to; as he passes through the various stages of his evolution, he finds himself before succeeding problems of adaptation to an external regimen with regard to food and sleep and habits of the toilet, problems of adaptation to external restrictions as to his utter-

1. Jung, C. G.: Ueber Konflikte der kindlichen Seele, *Jahrb. d. psychoan. u. psychopath. Forsch.*, 1910, ii, 33.

ances and behavior, of adaptation to the conflicting demands of the other self-assertive individuals who make up his world. With regard to each successive problem the child may show a constitutional difficulty of adaptation, a tendency to a neurotic persistence in the earlier phase; and each topic has its own familiar group of symptoms, which it would take us too far to review.

NEUROTIC UTILIZATION OF SYMPTOMS

So far we have discussed the origin of symptoms, and have emphasized the fact that symptoms may in some cases be the resultant of an internal conflict, a sort of compromise between the opposing forces in the patient's complex personality, an attempted solution of a strained situation in domestic politics.

We now pass over to the sphere of foreign politics, and consider the rôle which symptoms may play in enabling the child to dominate the environment. That rôle may be important to estimate if we wish to handle the situation judiciously. Symptoms may arise in various ways; they may be the result of a personal compromise, or they may be the expression of a nervous instability which needs no special conflict to elicit them, or they may even be the product of some casual somatic disorder; once they have arisen they may serve a certain function, and be made use of for the adaptation of the individual to the environment. Symptoms, whether of neurotic or other origin, are liable to be utilized by the neurotic child. In taking up the discussion of this topic, the endeavor again will be to exemplify in detail our conception in relation to a very limited number of symptoms, rather than to cover in a more general way a wide variety of symptoms.

Among the gastric symptoms presented by neurotic children vomiting is not uncommon and in some cases this symptom forms a very serviceable help to the child for the attainment of his ends. In both the following cases the neurotic symptoms of the child were fostered by the neurotic mother; what is laid at the door of heredity may often with more justice be attributed to the influence of the neurotic atmosphere supplied by the mother.

R. N., a boy of 17, was hardly able to read and write, but showed a surprisingly good reaction to the standard intelligence tests. His apparent backwardness was due to the almost complete neglect of school education, which was only partly justified by earlier sickness. His parents had tried on several occasions to send him to school; he then complained of headache and vomited when he was only a few yards from the house. The father one day insisted on the boy going to school, but the boy fell on the road as if in a faint, and was immediately rescued by the solicitous mother; from that date no further attempt at education was made and the boy remained in an exaggerated dependence on his mother, which pleased her very much. At 17 he used to climb on his mother's lap, and to say that he wanted to remain "mamma's baby," and that he did not want to grow up. The mother had

fostered in the child an attitude which was extremely strong in herself. She felt that a thread connected indissolubly the life of her mother, of herself, and of her child so that if one died the others would necessarily die. She said that evidently the child inherited his love for her; she herself had loved her parents so much that she cried for two years after she was married, until her parents came to live with her.

The neurotic parent is seldom willing to see her share of responsibility for the difficulties of the child; in order to understand the difficulties of the child, it would first of all be necessary to face honestly one's own difficulties and understand one's own life. Fortunately the mother was sufficiently cooperative for the boy's general hygiene to be put on a completely different basis; he made quick progress in his studies, but whether he will be successfully weaned is a very doubtful matter.

In another case where the situation was very similar, the vomiting had a more direct reference to dietary matters.

The patient, an only son of 9, was very capricious as to his diet, he would take only what he liked, and no more than he liked; he would accept milk only if flavored with coffee; as a rule he demanded steak for dinner. If his mother urged him to take more of some dish he would say, "I will vomit if you make me take another spoonful," and he kept his word.

Headache is another symptom which the child, as well as the adult, finds easily at his disposal in the face of unpleasant situations. It is frequently extremely difficult to determine how far we are dealing with headache of quite independent origin, or how far it is part of an unhygienic adaptation. The difficulty is increased when we are dealing with a girl subject to recurrent headache and gastric symptoms, whose mother is subject to megrim, a markedly hereditary disorder. It is extremely probable that in a certain number of such cases neurotic headache masquerades as inherited megrim.

Of the nervous manifestations of childhood, none are more alarming than the various attacks which are liable to occur. The diagnosis of epilepsy is often difficult and it is well to keep in mind the possibility that an attack, even though presenting some of the features of an epileptic equivalent, may really form part of a subtle mechanism by which the child attains a desired goal.

In the following case the rather complicated attacks seemed to express the dissatisfaction of the boy with his situation, and led to his getting the desired change, after which the attacks ceased.

G. J., a colored boy of 11, was referred from the Harriet Lane Home to the dispensary of the Phipps Clinic, May 28, 1915. The patient had been having very frequent "convulsions" since one day early in February, 1915, when he had been struck on the head by a baseball, without, however, being rendered unconscious. On the evening of the injury he was said to have vomited two long worms, and during the night he had several "convulsions." From that date he continued to have attacks several times a day; in these

attacks he behaved in a peculiar way, he used to bite, snap, froth, sing, run about and appear to converse with imaginary people, for example, his dead mother. He used finally to fall down. Before the attack his head felt heavy and dizzy, he felt as if he had to eat something; he did not remember his conduct during the attack, but said that after it he felt weak and drowsy.

These attacks might have been considered as atypical epileptic equivalents of traumatic origin; they appeared, however, to bear a striking relation to the situation. The boy was living in the country with his aunt and uncle and was very anxious to come into town; his attacks apparently made it very difficult for his aunt to keep him in the country. The boy himself put the matter very naïvely; "It's no wonder I'm having spells, I can't see much; nothing to keep my mind going; there's something to keep my mind going all the time in the city; if any one speaks rough to me it just seems if my head were coming off my shoulders; I want something to play with to keep my mind going; there's nothing to do but go out and play in the dirt." During the patient's stay in the Harriet Lane Home (April 2 to April 10, 1915), no convulsions were observed; the physical examination was practically negative. He was readmitted to the hospital on April 26, 1915, as the attacks had reappeared on his return to the country. No convulsions were observed in the hospital. Arrangements were made for the boy to live with his father in the city and since being in the city the attacks have ceased.

The exact origin and nature of these attacks may be difficult to explain, but there seems to be no doubt that they were utilized by the child for his own purposes to obtain a desired result; how far such utilization is subconscious or how far there may be some deliberate cultivation of the attacks is difficult to determine.

In the following case there was not the same obvious gain derived from the symptoms:

B. M., a colored boy of 10, was referred to the dispensary of the Phipps Psychiatric Clinic from the Harriet Lane Home on Oct. 25, 1915. After a normal infancy he began at the age of 3 years to have, once or twice a year, "spells of weakness" lasting for a few minutes. These were described as a "limpness of the body giving way." "You could tell the spell was coming on, he would get quite limp, and would fall, he would groan for a few minutes and then get up." During the earlier attacks he would attempt to answer questions, and would complain of feeling bad. In the later attacks there was more difficulty in answering questions. For the past two years he had about three or four attacks a year; there never was a preliminary cry, he never hurt himself in falling, he never wet or soiled himself during the attacks. Sept. 14, 1914, he had an attack in which he fell in a field; he was carried into the house and placed in bed, where he groaned and moved about uneasily for about ten hours. During the winter he had two attacks.

In September, 1915, his mother at breakfast said that she was feeling bad; he said, "I feel bad too, my head feels numb and dead." After breakfast his mother told him and his sister to wash the dishes; he said he couldn't as he had pains in the stomach. When his mother insisted, he went into another room, lay down on the lounge, and ten minutes later was found on the floor rolling as if in agony; he fought his father off, and could not respond clearly to questions. For two days he continued in perpetual motion, rolling in his bed and crawling out of it. He talked of wanting to go on a blue train, he clamored to go to Columbia. He slept well at night; in the morning he resumed his thrashing around, but would pause when spoken to. He knew his father, but for several days did not seem to know his mother or the other members of the family. This "violent state" lasted for eight or ten days, after which he became quiet, although he still talked in a "flighty" way.

Apart from these episodes the boy had shown no evidence of nervous instability; he gave no trouble as to his food or sleep, there was no bed-wetting or night-terrors. In his relationship to the other members of the family he had shown no specially intense attachments.

The child had been accustomed from the age of 3 or 4 years to go once a year to camp-meeting; he himself was a "great preacher round home," he would perform before other children with much unction and was applauded for his imitations of the convulsive movements of the ecstatic.

Although nothing in the situation seemed to explain the attacks, the boy's obvious desire to impress his comrades and the prestige derived from his own peculiar attacks seemed to have much to do with their origin; and the development of an attack in face of an unpleasant task seemed to favor this conception of the disorder.

The utilization of symptoms in a neurotic manner can not be more clearly exemplified than in the contrast between the two following cases, in which the symptoms consisted of involuntary movements. In one case we see the way in which a symptom, casually occurring in a child of good constitution, and correctly treated by the environment, passes without leaving a trace; while in the other case a similar symptom, perhaps of equally casual origin, is made use of by the neurotic individual and elaborated into a rather striking clinical phenomenon.

In the first case we have an experience, described by Scholz,² which happened to himself when he was 10 years old. One day just before the writing lesson his right hand began to tremble, he could only make illegible scrawls, and with a certain pride he demonstrated the symptom to the teacher. The latter paid no attention to it, a little to the boy's chagrin, and his father, a physician, treated the matter as of no interest. The tremor never reappeared.

Contrast this with the following case of a school girl reported by Jung:³

In the second year of school in the writing class, which she disliked, her right hand began to twitch; soon she was unable to write, and had to give up the class. The involuntary movements spread and became general, a "hysterical chorea;" owing to these symptoms and to morbid fears her attendance at school was very irregular and at 12 was completely discontinued. On the onset of menstruation at the age of 15 the involuntary movements abruptly ceased, and were now replaced by a variety of other hysterical symptoms.

Here we see how a girl of poor nervous balance, which showed itself later in a variety of hysterical symptoms, had at an early age utilized apparently involuntary movements for a definite end. When the patient looked back on this period she realized that she had culti-

2. Scholz, L.: *Anomale Kinder*, p. 152.

3. Jung, C. G.: *Diagnostische Assoziationstudien*, ii, 31.

vated the disorder; she admitted that she could have controlled the movements if she had exerted herself and that it suited her to be sick.

It is probable that in some cases the relapses after a Sydenham's chorea represent, not a return of the previous condition, but the neurotic utilization of symptoms which the previous sickness has made familiar.⁴

ORIGIN OF NEUROTIC SYMPTOMS IN GENERAL

So far we have discussed two main topics. The first related to the fact that familiar symptoms may be the indicators of conflicts in the child's life, the presence of which is often not suspected; the recognition of these conflicts is important for the treatment of the child. The second topic was the way in which various symptoms, no matter what their origin, may be utilized by the neurotic child; it is necessary to recognize the circumstances which tend to foster the symptoms, if the situation is to be put on a hygienic basis. If the symptoms are utilized in the adaptation of the child to its environment, it is not meant thereby that the child does so clearly and deliberately; we are dealing with a biological adaptation in which conscious purposes may play a very subordinate, even a vanishing, rôle.

A third topic remains for discussion, namely, the origin and nature of neurotic symptoms in general, quite apart from their later utilization or the conflicts which in some cases they may indicate. The fact that a symptom may in some cases be utilized in a certain way, and may indicate personal conflicts, does not entitle us to conclude that in every case it is so utilized, and that it must always indicate such conflicts. There may be other cases in which the same symptoms are elicited by a great variety of causes as the expression of a constitutional instability. They would then be a measure of the nervous stability of the child, and their practical importance would consist in the indication that the child with such symptoms may not be able to meet the same stress and strain as his fellows, and may require certain special safeguards.

One of the earliest of such symptoms is that the infant is extremely easily startled; disorders of sleep may also be pronounced at an early age; other symptoms are an exaggerated conservatism with regard to diet, the refusal to be weaned and to make the regular progress up the dietary ladder; anomalies as to micturition and defecation may be met with; the child may show apparently capricious but determined refusal to pass water or to have movements at suitable times, and an apparent constipation may represent an early form of self-assertion, which may yield to coaxing or a whipping; vomiting, headache, chorei-

4. Thiemich, M., and Zappert, J.: *Die Krankheiten des Nervensystems im Kindesalter*, p. 193.

form movements, stammering, tics, and habit-movements have to be considered; while a great variety of attacks may occur varying in severity from the familiar tantrum of temper to epileptiform convulsions.

This list of symptoms is by no means complete and each symptom presents many special problems. Here again only a very few symptoms will be discussed.

As to the disorders of sleep, reference has already been made to the complex determinants which may be at the basis of some cases of sleeplessness. The night-terror (*pavor nocturnus*) so frequent in children may occur in a very complex setting as in the case of the 7-year-old boy described above and in the 4-year-old girl described by Jung. But it is important to recognize that night-terrors may arise in a very simple setting and may not indicate more than a vague nervous tension which we have difficulty in analyzing further. Thus Miss Shinn,⁵ in her charming description of the development of her niece, notes at the end of the fourth month an early indication of this phenomenon, and a still more definite episode at the seventh month. In some cases overstimulation before bedtime, especially emotional stimulation, such as is supplied by moving pictures, seems to be responsible for the symptom. Strohmeyer⁶ calls attention to the fact that in some cases the symptom is related to the nascent sexual instinct, which may be partly aroused by overcaressing and carelessness with regard to the sleeping arrangements. While the night-terror is as a rule a benign symptom, it may have a more dread significance, it may be an epileptic equivalent. This is considered by Aschaffenburg⁷ to be probable if the symptoms are accompanied by bed-wetting and if the child remains dull and confused for more than a few minutes, notwithstanding efforts to arouse him. Thiemich,⁸ however, lays no such stress on a much longer period of confusion and considers the connection with epilepsy extremely rare.

In the following case the symptoms seemed to be partly related to a very emotional experience which the imaginative child had undergone:

J. S., a boy of 8, Feb. 6, 1915, was referred from the Harriet Lane Home to the dispensary of the Phipps Psychiatric Clinic on account of night-terrors. The patient would wake up in a panic and for a period of fifteen or twenty minutes or longer would see imaginary animals and talk in distress about frogs, turning wheels, cannibals, etc.; the symptoms had begun at the age of 6; in the earlier attacks he would, after coming to himself, pass urine and

5. Shinn, M. W.: *The Biography of a Baby*, p. 195.

6. Strohmeyer, W.: *Vorlesungen über die Psychopathologie des Kindesalters*, p. 25.

7. Aschaffenburg, G.: *Der Schlaf im Kindesalter und seine Störungen*, p. 20.

8. Thiemich, M., and Zappert, J.: Footnote 4, p. 219.

go off to sleep. Of late the boy had wet the bed during these attacks; and, in addition to the night-terrors, he would occasionally in the afternoon become pale, and speak incoherently for fifteen to twenty minutes, referring to peculiar shadows or figures which he saw.

The boy had shown no nervous symptoms until the age of 6. At that age the mother wished to punish him, but thought a whipping would have little effect; she therefore put him down in the cellar, where she assured him the rats would eat him. He was much upset and owing to his screaming he was released in two minutes; he played about for an hour and then fell asleep. On waking from his sleep he started to scream, said that he saw rats and frogs and people. From that time the boy was troubled with bad dreams, in some of which he dreamed of rats. When he was asked whether any incident had ever occurred to make him dream of rats, he made no reference to the above episode. He tended to weave any recent dramatic experience into his dreams, which were peopled with the heroes of the moving pictures. The boy was of an unusually imaginative disposition, he was already a poet, and this trait may explain the quasihallucinatory phantasies in the daytime. Thus, he made reference to an imaginary boy smiling at him and to rather mysterious "chills" or clouds of smoke, which he saw or conjured up. "I think I see them a little now, chills, clouds of smoke . . . when I think of them, I can hardly forget it . . . it seems just like clouds of smoke, I don't really see them but I think of them and that makes me a little bit just like I see them. . . . I hollered out to mamma to stop them people, they were stealing the smoke . . ."

These utterances were rather a contrast with the frank, healthy appearance of the red-cheeked urchin; as a matter of fact, two weeks later the boy was already sleeping very much better, and the bad dreams and fantastic "chills" have been practically absent since that time. One further trait of the boy may be mentioned; in kissing his mother he had a habit of biting her. "I try to kiss but I can't; I just bite a little bit; I can't help it." He would kiss his little sister, however, without biting her. Notwithstanding the hallucinatory confusion, the bed-wetting, the afternoon attacks, in this case it is doubtful whether epilepsy has to be seriously considered.

An emotional episode seemed to precipitate the symptoms and to give them a certain color, but a similar picture can develop with no such apparent cause and we are bound to lay the stress on the constitutional nervous instability of the patient.

Bed-wetting (enuresis nocturna) is another very common sign of nervous instability. In some cases it is the response to a rather complicated situation, as in the case of a boy of 5 who showed marked increase of bed-wetting, occasional soiling and night-terrors, when removed from his mother and placed in an orphanage; when placed again with his mother the condition showed immediate improvement. The frequent connection of bed-wetting with masturbation is noted by Strohmeyer.⁹ In many cases, however, there is no trace of any of the above factors, and the symptom has merely the value of a neurotic indicator.

The vomiting of neurotic children may arise on the same general basis of neurotic instability; thus in the cyclic vomiting of children the symptom may develop where no special conflict can be discovered, and

9. Strohmeyer, W.: Footnote 6, p. 55.

the symptom seems to form part of no neurotic adaptation. It is not necessary to assume that the mechanism of the symptom is always as complex as in the cases reported above of the neurotic utilization of the symptom, or in cases such as that of Strohmeyer, in which the vomiting ceased after the child had talked over his masturbation with the physician and received reassurances from him.

Choreiform movements may represent the hysterical expression of repressed factors, and may be utilized in a neurotic way, as in the case of Jung, referred to above. In a great many cases choreiform movements seem to play a much less definite rôle and to have an explanation at a simpler biological level. They occur in a large number of children who show evidence of general constitutional inferiority, and they may represent a special type of motor inferiority going parallel with the inferiority which is present in the intellectual and the emotional life. Choreiform movements need not be associated with mental defect, but may simply be the indication of a rather special type of nervous instability.

Among the indicators of nervous instability sexual activities have attracted much attention. The exact rôle which the sexual instinct plays in the development of nervous manifestations in the child and in the adult is a subject of much debate, often rather acrimonious; the tendency undoubtedly in the past has been for us to overlook many of its manifestations, influenced by the altogether too simple conventional conception of the life of the child. Before considering, however, various symptoms as secondary to sexual activities, we have to recognize that the precocious development of these interests and activities and a disproportionate prominence of certain elements in these complicated functions are in themselves evidence of a neurotic instability, except in cases in which unfortunate external circumstances have forced the development of instinct. Thus precocious and excessive masturbation has to be looked on as evidence of nervous instability, as a symptom, and not only as a cause, of nervousness; and, in estimating the further nervous symptoms of the individual child, it may be difficult to know how far these are directly related to the sexual activities, or how far they draw their origin from a common source, from the underlying constitutional instability. It is extremely important that these factors should be estimated at their correct biologic value, and dealt with according to sound hygienic principles and not according to narrow inappropriate ethical standards. An open and healthy atmosphere will perhaps spare the neurotic child the development of methods of adaptation which may handicap the whole of the adult life.

A separate chapter would be required for a discussion of the various attacks which occur in nervous children. The exact relationship of many of these attacks to spasmophilia on the one hand and to epilepsy on the other is a problem of very great importance. In the individual case it may be difficult to draw the line between tantrums of temper in a neurotic child and spasmophilic attacks. Nor is it clear how far we should include under spasmophilia all those episodes in neurotic children, precipitated by definite emotional causes which we are not entitled to refer either to hysteria or to epilepsy, episodes to which Bratz¹⁰ has given the name of *affektepileptische Anfälle*, and which are referred to under a great variety of names by other authors. Among these attacks may be instanced Wegbleiben (as in the case of T. A.), narcolepsy, attacks of vertigo and fainting, and attacks similar to petit mal and grand mal.

Further work on these disorders may enable us in a certain number of cases to formulate the constitutional inferiority of the individual in definite biochemic and physiologic terms, and may reduce considerably the number of those cases in which we are still forced to employ such general terms as constitutional nervous instability or neuropathic constitution. If in the preceding part of our paper we have emphasized the importance of the wider psychobiologic attitude for the proper understanding of neurotic symptoms, in the present sphere we are dependent on the researches of the pediatricist, employing biochemic and physiologic methods.

SUMMARY

The study of the psychoneuroses of the adult has thrown a good deal of light on the complexity of the life of the child; conflicts analogous to those of the adult are present in childhood, and may give rise to the same types of nervous disorder. The neurotic child may show at an early age difficulty in passing from one stage of adaptation to another, a tendency to retain the attitude of the earlier stage, an incomplete assimilation of the more mature attitude.

Familiar symptoms may indicate the presence of such a difficulty in the child's adaptation and the recognition and treatment of the difficulty will depend on a just appreciation of the complexity of the child's life, a complexity which is alien to the conventional conceptions of childhood.

In the study of the rôle played by certain symptoms in childhood it is useful to remember that these symptoms may be a method by which the child, more or less subconsciously, asserts himself and enjoys certain immunities or privileges.

10. Bratz, Emil: Die affektepileptischen Anfälle der Neuropathen und Psychopathen, Monatschr. f. Psychiat. u. Neurol., 1900, xxix, 45, 162.

Although certain symptoms may arise in a very complex manner and persist owing to their utility, they need not have such complex significance; they may, as the indicators of a constitutional nervous instability, be elicited by a great variety of causes. The pediatricist, by the application of accurate methods to the study of these early symptoms, may contribute to psychopathology a much clearer formulation of the basis of some types of nervous constitution.

I take this opportunity of thanking Dr. Howland for his help in the preparation of this paper, and for placing at my disposal the pediatric records of several of the cases referred to.

THE EFFECT OF COLD AIR ON THE BLOOD PRESSURE IN PNEUMONIA IN CHILDHOOD *

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Largely as the result of the enthusiastic endorsement of Northrup¹ of New York in a series of papers on the subject, published between 1904 and 1906, the cold-air treatment of pneumonia has been more or less completely adopted by most pediatricians and by many practitioners. No very satisfactory explanation for the supposedly beneficial results of this method of treatment was advanced, however, in the beginning.

Howland and Hoobler,² writing in 1912, stated that it was apparent that children seriously ill with pneumonia might have a blood pressure somewhat below what might be expected at their age, and that the symptoms of the death of children from pneumonia were those of vasomotor failure. They found that the effect of cold, fresh air in patients with active pneumonia was always to produce a rise in blood pressure. Removal to a warm (65 F.) room produced a fall in blood pressure. The results were absent or much less striking in convalescents. They were unable to get any results by putting children out of doors in warm weather. They concluded, therefore, that the all-important factor in the out-of-door treatment was cold, and that the rise in blood pressure was brought about by a reflex stimulation of the vasomotor center by the action of the cold air on the skin. They also stated that there is no doubt that an increase in the blood pressure, when it is abnormally low, which is constant and continuous and which is brought about without exhaustion or bad effects, is of the greatest value. This explanation of the beneficial effects of the outdoor treatment was generally accepted.

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1. Northrup: *Med. News*, 1904, lxxxiv, 823; *Chicago Med. Recorder*, 1904, xxvi, 628; *Med. Rec.*, New York, 1905, lxxvii, 253; *Boston Med. and Surg. Jour.*, 1906, cliv, 216; *Jour. Am. Med. Assn.*, 1906, xlvii, 1182; *Med. Jour.*, New York, 1907, lxxxvi, 12.

2. Howland and Hoobler: *AM. JOUR. DIS. CHILD.*, 1912, iii, 294.

About this time, however, Weigert³ published a paper in which he concluded, on the basis of his experience and from his study of the literature, that no rule can be established for the blood pressure in pneumonia, and that in consequence blood pressure readings are of no prognostic value. Newburgh and Minot,⁴ in 1914, from a study of a considerable number of cases, mostly in adults, found that the systolic pressure in the fatal cases was continuously above the systolic pressure in the persons who recovered. They concluded, therefore, that failure of the peripheral circulation cannot be a common cause of death in pneumonia. Porter and Newburgh⁵ have also recently shown experimentally that the vasomotor center is not impaired in fatal pneumonia in animals.

Freeman⁶ states, moreover, that Schloss, in work done under his supervision at the New York Foundling Hospital and at the New York Nursery and Child's Hospital, was unable to corroborate Howland and Hoobler's results, and that Hartshorn has carried out a considerable series of blood pressure experiments at the Roosevelt Hospital with no constant results. They found that while some children showed a considerable increase in blood pressure on being put out of doors, others showed no increase, while, on the other hand, there was no constant fall of blood pressure noted when the children returned to the ward. In fact, the blood pressure was no higher out of doors than in the ward.

Not being aware of the investigations of Freeman and his co-workers and having been struck with the fact that the results of Weigert, Newburgh and Minot, and Porter and Newburgh did not confirm those of Howland and Hoobler, the writers made a study of the effect of cold, out-of-door air on the blood pressure in pneumonia in childhood, at the Boston Children's Hospital during the past winter. There were made 387 observations on thirty-two children. The ages of these children varied between 2 and 10 years, nineteen of them being under 5 years of age.

Eight of the children died. The illness was classified as very severe in three, severe in fourteen, moderately severe in four and mild in three.

The methods employed in the investigation were as follows: The children were kept in the warm ward for a varying number of hours. They were then put out of doors for a varying number of hours, brought back into the ward again, put out again, and so on, until after the crisis occurred or the child died. The blood pressures were taken at the end of each period, that is, just before going out of doors when the child had been in the ward for some hours, and just before coming

3. Weigert: *Samml. klin. Vort.*, 1911, 459.

4. Newburgh and Minot: *Arch. Int. Med.*, 1914, xiv, 48.

5. Porter and Newburgh: *Am. Jour. Physiol.*, 1914, xxxv, 1.

6. Freeman: *Am. Jour. Med. Sc.*, 1916, cli, 1.

into the ward after it had been out of doors for some hours. The Tyco's sphygmomanometer was the instrument employed. The width of the cuff was four and one-half inches. Except in a few instances the right arm was always used for taking the pressures. The readings of the blood pressures were made at the ends of the second and third phases, that is, after the pulse was obliterated (first phase) the systolic reading was made at the first hard thump following the few dull thumps of the second phase. The diastolic reading was made at the end of the third phase, at the time when the definite change from the hard thump to the dull thump of the fourth phase occurs.

The protocols give the data in each case in detail. The temperature readings are in the Fahrenheit scale. "Ent." means at entrance. "In" means that the readings were taken at the end of the time spent in the ward, and "out" that they were taken just before the child was taken in from being out of doors.

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Dis- ease	Out- doors or In	Hours	Temp- erature of Place	Pulse	Res- pira- tion	Blood Pressure		
							Sys- tolic	Dias- tolic	Pulse
No. 6528 Age, 2½ years Left lower lobe, severe	3	In	Ent.*	72	130	40	100	65	35
		Out	2	50	125	35	98	60	38
		In	2	70	130	40	103	67	36
		Out	2	50	120	30	100	65	35
		In	1	74	115	35	102	64	38
		Out	1	54	110	30	100	65	35
	4	Out	12	52	120	40	105	70	35
		In	1	68	110	35	110	75	35
		Out	1	54	115	40	105	70	35
		In	1	72	115	40	105	68	37
		Out	1	54	130	38	104	70	34
		In	3	70	125	40	100	65	35
		Out	3	50	120	35	110	75	35
	5	Out	15	60	140	40	118	80	38
		In	1	72	137	38	115	75	40
		Out	2	50	145	40	118	78	40
		In	2	82	150	45	106	63	43
		Out	2	48	160	50	105	60	45
		In	2	76	130	45	105	60	45
	6	Out	12	54	115	30	108	70	38
		In	1	68	115	30	105	65	40
		Out	2	52	120	30	100	60	40
		In	2	78	118	32	105	65	40
		Out	2	52	115	30	104	64	40
		In	1	78	130	42	100	60	40
	7	Out	14	50	120	32	102	58	44†
		In	2	72	115	30	102	56	46

* Ent. means at entrance. The temperature readings are in the Fahrenheit scale. The tyco's sphygmomanometer was used with a four and a half inch cuff. All blood pressures were taken at end of periods In or Out, or in other words, just before changing from warm to cold, or vice versa. Except in a few instances, the right arm was used for all pressures. Blood pressure readings were made at the ends of the second and the third phases, that is, after the pulse is obliterated (first phase) the systolic reading is made at the first hard thump following the few dull thumps of the second phase. The diastolic reading is made at the end of the third phase or where there is a perceptible drop from the hard thump to the dull thump of the fourth phase.

† Crisis.

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Dis- ease	Out- doors or In	Hours	Temp- erature of Place	Pulse	Res- pira- tion	Blood Pressure		
							Sys- tolic	Dias- tolic	Pulse
No. 6546 Age, 6½ years Left lower lobe, mod. severe	4	In	Ent.	70	135	43	85	60	25
		Out	2	45	130	45	95	55	45
		In	3	75	120	32	98	55	43
		Out	2	42	118	30	95	50	45
	5	Out	14	40	80	25	95	45	50†
		In	3	70	100	23	100	55	45
No. 6559 Age, 7 years Left lower lobe, severe	5	In	Ent.	70	105	48	98	60	38
		Out	2	40	120	38	105	55	50
		In	2	70	120	42	108	60	48
		Out	2	42	90	42	108	58	50
	6	Out	14	36	90	25	95	53	42†
No. 6629 Age, 3 years Right upper lobe, very severe	4	In	Ent.	70	128	40	113	85	28
		Out	2	42	120	40	100	60	40
		In	3	70	132	35	100	65	35
		Out	3	40	128	35	98	60	38
	5	Out	15	38	128	40	98	60	38
		In	2	70	120	35	95	55	40
		Out	3	50	128	35	95	55	40
		In	4	70	132	38	88	50	38
	6	Out	12	40	130	40	90	52	38
		In	4	65	120	36	92	54	38
		Out	4	50	118	34	92	55	37
		In	2	70	120	40	90	52	38
	7	Out	12	45	130	35	88	50	38
		In	4	70	135	40	90	54	36
		Out	4	45	130	38	82	45	37
		In	3	70	140	42	85	45	40
	8	Out	12	45	100	35	75	40	35†
		In	12	65	110	32	90	50	40
No. 6611 Age, 7 years Right lower lobe severe	7	In	Ent.	70	160	40	95	50	45
		Out	3	40	120	55	85	55	30
	8	Out	15	40	110	30	80	40	40
		In	2	70	120	42	78	40	35
		Out	4	42	130	40	80	40	40
		In	4	65	130	50	82	42	40
	9	Out	12	38	120	36	80	40	40
No. 6614 Age, 2¼ years Left lower lobe, mild	3	In	Ent.	70	162	38	80	40	40
		Out	3	40	150	40	75	38	37
	4	Out	15	40	130	36	83	40	43†
		In	4	62	110	32	82	42	40

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR
TREATMENT

Number, Age, Nature of Disease	Day of Dis- ease	Out- doors or In	Hours	Temp- erature of Place	Pulse	Res- pira- tion	Blood Pressure		
							Sys- tolle	Dias- tolle	Pulse
No. 6435 Age, 3 years Right and left lower lobes, very severe	7	In	Ent.	70	165	38	95	70	25
		Out	2	40	150	38	95	65	30
	8	Out	14	34	132	40	93	58	35
		In	2	68	138	43	92	55	37
		Out	3	42	150	32	95	55	40
		In	3	70	160	40	80	60	20
		Out	3	42	168	42	78	50	28
		In	4	64	180	48	85	50	35
	9	Out	12	40	165	43	85	50	35
		In	2	70	162	40	88	60	28
		Out	3	50	160	52	88	62	26
		In	2	70	180	55	82	54	28
		Out	2	50	180	55	78	?	?
		Patient died several hours later, no blood pressure obtainable shortly before death (stimulation)							
No. 6628 Age, 8 years Left lower lobe, mod. severe	2	In	Ent.	65	120	37	100	70	30
	3	Out	12	40	130	43	100	50	50
		In	2	70	120	30	98	55	43
		Out	2	45	120	30	95	50	45
		In	4	72	130	30	98	48	50
		Out	3	40	125	28	95	55	40
	4	Out	15	40	132	43	88	48	40
		In	2	70	130	45	90	52	38
		Out	2	45	128	40	85	42	43
		Out	5	38	132	42	88	47	38
		In	4	70	120	48	90	45	45
	5	Out	12	35	98	32	90	50	40
		In	2	70	112	40	88	52	36
		Out	4	35	110	38	94	60	34
		In	3	70	100	40	85	50	35
		Out	2	40	85	30	80	50	30;
	6	Out	14	40	70	23	84	50	34
		In	2	70	75	25	82	50	32
No. 6563 Age, 5½ years Left lower lobe, mod. severe	2	In	Ent.	70	120	48	125	80	45
		Out	2	40	130	45	120	80	40
	3	Out	14	36	140	48	118	78	40
		In	2	70	140	42	118	75	43
		Out	2	40	142	38	115	75	40
		In	2	68	110	40	118	78	40
		Out	3	42	115	35	122	80	42
		In	2	72	122	36	124	80	44
	4	Out	12	40	112	38	115	70	45
		In	2	68	128	40	113	70	43
		Out	3	40	140	40	125	80	45
		In	5	70	143	48	120	80	40
	5	Out	12	40	105	32	128	82	46
		In	2	70	110	30	118	80	38

‡ Lysis

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Dis- ease	Out- doors or In	Hours	Temp- erature of Place	Pulse	Res- pira- tion	Blood Pressure		
							Sys- toleic	Dias- toleic	Pulse
No. 6427 Age, 3½ years Left lower lobe, severe	2	In	Ent.	70	130	40	100	60	40
		Out	4	40	135	42	84	60	24
		In	2	70	142	55	86	58	28
	3	Out	12	40	132	40	94	55	39
		In	2	68	134	38	92	56	36
		Out	2	38	130	34	92	54	38
		In	3	72	120	30	90	50	40
		Out	3	40	126	34	92	55	37
	4	Out	15	40	132	40	96	50	46
		In	4	72	132	45	95	48	47
	5	Out	12	45	132	40	100	58	42
		In	2	70	138	46	94	50	44
		Out	2	42	132	42	92	54	38
		In	5	70	128	38	88	44	44
		Out	2	40	130	42	90	48	42
	6	Out	14	38	108	40	104	60	44
		In	3	70	115	38	98	55	43
		Out	4	45	120	40	95	55	40
		In	3	72	128	43	92	50	42
		Out	2	50	135	47	90	50	40
		Out	14	45	108	35	88	55	33†
No. 6547 Age, 4 years Left lower lobe, very severe	13	In	Ent.	65	175	68	85	40	45
		Out	2	40	190	80	82	48	34
				Died two hours later (stimulation)					
No. 6535 Age, 10 years Right upper lobe, severe	2	In	Ent.	70	160	45	108	80	28
		Out	3	35	150	42	95	65	30
		In	3	70	150	42	92	72	22
		Out	2	38	90	50	40
	3	Out	14	35	162	40	90	60	30
		In	2	70	100	70	30
		Out	4	42	150	50	75	50	25
		In	2	72	190	62	78	50	28
				Died one hour later (stimulation)					
No. 6620 Age, 5 years Whole right lung	10	In	Ent.	65	160	40	90	50	40
				Died two hours later (stimulation)					
No. 6561 Age, 6 years Both lower lobes	6	In	Ent.	70	128	38	135	110	25
				Died one hour later (stimulation)					
No. 5965 Age, 5 years Right upper lobe	2	In	Ent.	72	130	67	98	46	52
	3	Out	12	42	140	82	65	30	35
				Died less than an hour later (stimulation)					

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR
TREATMENT

Number, Age, Nature of Disease	Day of Dis- ease	Out- doors or In	Hours	Temp- erature of Place	Pulse	Res- pira- tion	Blood Pressure		
							Sys- tolic	Dias- tolic	Pulse
No. 6740 Age, 2½ years Both lower lobes, very severe	8	In	Ent.	70	120	32	82	50	32
	9	Out	12	20	175	60	102	60	42
		In	5	60	200	80	84	50	34
		Out	4	30	160	60	80	40	40
		In	5	54	165	80	84	35	49
		Death several hours later (stimulation)							
No. 6693 Age, 3½ years Right upper lobe, very severe	4	In	Ent.	70	142	60	105	60	45
	5	Out	12	40	135	62	92	50	42
		In	4	75	105	65	40
		Out	4	35	108	65	43
		In	3	72	148	52	118	65	53
	6	Out	12	30	135	48	94	50	44
		In	4	70	158	60	98	56	42
		Out	4	38	90	50	40
		In	2	70	155	55	94	55	39
		Out	2	35	150	53	90	50	40
	7	Out	14	32	120	34	90	56	34
		In	4	72	112	43	94	50	44
		Out	4	38	115	40	100	54	46
		In	3	72	110	35	102	48	54
	8	Out	12	24	120	37	85	45	40†
No. 6749 Age, 2 years Left lower lobe, severe	3	In	Ent.	72	155	32	84	43	32
		Out	2	35	150	33	80	52	23
		In	2	70	150	45	84	50	34
	4	Out	12	30	140	52	90	60	20
		In	4	70	135	55	90	56	34
		Out	4	30	128	60	84	50	34
		In	3	68	135	50	78	42	36
	5	Out	12	30	128	35	80	45	35†
No. 6760 Age, 4 years Right lower lobe, severe	4	In	Ent.	72	158	53	74	42	32
		Out	4	35	140	57	78	40	33
		In	4	72	132	48	78	42	36
	5	Out	12	32	112	40	80	46	34
		In	4	70	128	43	96	54	42
		Out	3	35	180	60	100	48	52
		In	3	68	148	50	90	45	45
	6	Out	12	32	125	48	90	54	36
		In	4	72	125	48	75	38	37
		Out	3	34	120	48	74	42	32
		In	4	72	162	60	70	40	30
	7	Out	12	28	135	60	82	50	32
		In	4	70	120	48	78	46	32
		Out	4	35	122	48	78	44	34
		In	4	68	132	52	78	40	33
	8	Out	12	28	130	32	76	44	32†

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Dis- ease	Out- doors or In	Hours	Temp- erature of Place	Pulse	Res- pira- tion	Blood Pressure		
							Sys- tolic	Dias- tolic	Pulse
No. 6787 Age, 2¾ years Left lower lobe, severe	3	In	Ent.	68	135	60	82	54	28
	4	Out	12	40	120	40	76	52	24
		In	4	70	74	54	20
		Out	3	45	74	56	18
		In	3	70	120	37	76	56	20
	5	Out	12	40	142	52	72	54	18
		In	4	72	72	43	29
		Out	4	42	70	45	25
		In	4	70	144	48	70	45	25
	6	Out	12	40	144	48	68	42	25
		In	4	78	70	38	32
		Out	4	45	72	38	34
		In	4	72	130	43	72	39	33
	7	Out	12	40	130	40	68	40	28
		In	4	72	74	42	32
		Out	4	40	72	40	32
		In	4	70	122	38	72	42	30†
		Out	12	40	108	32	70	38	32
No. 6797 Age, 3½ years Right lower lobe, severe	2	In	Ent.	65	142	60	68	40	28
		Out	4	50	72	45	27
		In	4	70	168	65	70	42	28
		Out	2	50	70	44	26
		In	2	70	69	42	27
	3	Out	12	42	142	64	68	40	28
		In	4	72	68	35	33
		Out	4	50	78	56	22
		In	4	70	158	80	94	64	30
	4	Out	12	45	145	62	88	60	28
		In	4	70	140	58	84	60	24
		Out	4	50	86	64	22
		In	4	70	145	54	88	63	25
	5	Out	12	42	142	63	68	34	34
		In	4	72	78	42	36
		Out	4	40	82	42	40
		In	4	70	144	62	80	50	30
	6	Out	12	40	150	57	66	38	28
		In	4	70	72	43	29
		Out	4	50	64	30	34
		In	4	70	162	82	62	32	30
	7	Out	12	35	115	50	60	36	24
		In	4	70	110	42	78	50	28
		Out	4	40	78	52	26†
		In	3	70	115	38	74	46	28
No. 6716 Age, 5 years Right lower lobe, mod. severe	8	In	Ent.	72	140	37	100	58	42
		Out	3	40	100	62	38
		In	3	72	145	42	100	60	40
	9	Out	12	35	140	32	102	63	39
		In	5	70	98	54	44
		Out	3	50	98	55	43
		In	4	72	145	48	100	60	40
	10	Out	12	40	140	35	94	58	36
		In	4	72	97	59	38
		Out	4	48	98	60	38
		In	4	70	148	48	100	58	42
	11	Out	12	40	100	24	98	60	38†

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Dis- ease	Out- doors or In	Hours	Temp- erature of Place	Pulse	Res- pira- tion	Blood Pressure		
							Sys- tolic	Dias- tolic	Pulse
No. 000? Age, 3½ years Left lower lobe, severe	4	In	Ent.	70	150	53	78	45	33
		Out	4	35	140	48	76	40	36
		In	4	72	136	37	76	42	34
	5	Out	12	32	140	42	78	48	30
		In	4	70	132	42	74	42	32
		Out	3	35	148	50	74	40	34
		In	3	68	148	43	70	40	30
	6	Out	12	35	140	38	72	38	34
		In	4	70	134	40	68	34	34
		Out	4	32	152	47	70	40	30
		In	4	70	135	32	68	36	32
	7	Out	12	30	160	48	70	40	30
		In	4	70	148	46	70	45	35
		Out	4	35	158	50	72	42	30
		In	4	70	140	43	70	40	30
	8	Out	12	28	150	36	68	36	32
		In	4	72	148	45	62	36	26
		Out	4	35	158	38	70	42	28
		In	4	70	108	40	72	38	34†
	9	Out	12	25	102	36	78	45	33
No. 6583 Age, 8 years Both lower lobes, severe	4	In	Ent.	70	160	80	85	40	45
		Out	4	50	145	70	82	45	37
	5	In	12	70	132	60	90	50	40
		Out	4	40	148	70	100	65	35
		In	4	72	148	62	100	62	38
		Out	2	32	135	62	98	59	39
		In	2	70	142	65	96	62	34
		Out	12	32	140	62	98	65	33
	6	In	4	70	145	63	100	65	35
		Out	4	35	142	62	95	60	35
		In	4	70	155	80	92	55	37
		Out	12	30	147	75	98	57	41
	7	In	4	70	120	70	100	58	42
		Out	4	35	110	68	100	60	40
		In	4	72	105	62	95	55	40
		Out	12	30	118	68	102	64	38
	8	In	4	68	120	72	98	62	36
		Out	4	35	118	72	90	50	40
		In	4	70	98	35	88	52	36½
		Out	12	30	92	40	85	54	31
		In	4	70	88	35	82	52	30
		Out	4	70	88	35	82	52	30

The blood pressure readings were taken 198 times after the child had been out of doors from one to eighteen hours, and 154 times after the child had been in from one to twelve hours. The results of these readings are shown in Tables 1 and 2.

TABLE 1.—BLOOD PRESSURES AFTER BEING OUT OF DOORS

	No.	Per Cent.
Rise in systolic pressure.....	63	31 +
Fall in systolic pressure.....	105	53
No change in systolic pressure.....	30	15 +
Rise in diastolic pressure.....	86	43 +
Fall in diastolic pressure.....	88	44 +
No change in diastolic pressure.....	24	12 +
Rise in pulse pressure.....	67	34 —
Fall in pulse pressure.....	101	51
No change in pulse pressure.....	30	15 +

TABLE 2.—BLOOD PRESSURES AFTER BEING IN WARD

	No.	Per Cent.
Rise in systolic pressure.....	65	42 +
Fall in systolic pressure.....	62	40 +
No change in systolic pressure.....	27	17 +
Rise in diastolic pressure.....	58	37 +
Fall in diastolic pressure.....	79	51 +
No change in diastolic pressure.....	17	11 +
Rise in pulse pressure.....	80	52 —
Fall in pulse pressure.....	55	36 —
No change in pulse pressure.....	19	12 +

It is evident from these tables that the temperature of the surrounding air had no constant effect on the systolic, the diastolic or the pulse pressure. It is further noteworthy that both the systolic and the diastolic pressure rose more often after the children had been in the warm air of the ward for some hours than after they had been out in the cold for a number of hours. Further analysis of the protocols shows that, whether the change was from warm to cold or from cold to warm, the variations in the blood pressure were as a rule slight and within the limits of possible errors in observation. It also shows that the variations in pressure bear no relation to the temperature of the outdoor air or the duration of the stay out of doors.

A study of the protocols in detail shows, moreover, that there was no definite relation between the systolic pressure, the diastolic pressure or the pulse pressure and the severity of the disease. Relatively high pressures and relatively low pressures, systolic, diastolic and pulse, were found in all types of the disease. No constant relations of any sort can be made out. These statements are equally true as regards the fatal cases.

The rates of the pulse and respiration were counted in many instances at the same time that the blood pressure was taken, to determine, if possible, what effect the temperature of the surrounding air had on them. The rate of the pulse was counted 166 times after the child had been out of doors for a number of hours, and 130 times after it had been in the ward for several hours. Tables 3 and 4 show the results of these observations.

TABLE 3.—PULSE RATE AFTER BEING OUT OF DOORS

	No.	Per Cent.
Increased	57	34 +
Diminished	97	58 +
Unchanged	12	7 +

TABLE 4.—PULSE RATE AFTER BEING IN WARD

	No.	Per Cent.
Increased	64	49 +
Diminished	52	40
Unchanged	14	10 +

These tables show that the temperature of the surrounding air had no constant effect on the rate of the pulse. In general, however, the tendency was for the pulse rate to be lower out of doors than in the ward. In many children, nevertheless, there was no relation whatever between the pulse rate and where the child was, the rate varying sometimes in one way and sometimes in the other. In a few instances the pulse rate was usually higher when the children were out of doors. The pulse rate was usually lower when the patients had been out for twelve hours or more than when they had been out but a few hours. There were, however, many exceptions to this rule. It must also be remembered that these long hours were almost always at night and that the pulse rate was taken in the morning after a long rest and at the time when the pulse rate is normally the lowest.

The rate of the respiration was counted 168 times after the child had been out of doors for a number of hours and 137 times after it had been in the ward for several hours. Tables 5 and 6 show the results of these observations.

TABLE 5.—RATE OF RESPIRATION AFTER BEING OUT OF DOORS

	No.	Per Cent.
Increased	49	29 +
Diminished	94	56
Unchanged	25	14 +

TABLE 6.—RATE OF RESPIRATION AFTER BEING IN WARD

	No.	Per Cent.
Increased	71	51 +
Diminished	58	42 +
Unchanged	8	6 —

These tables show that the temperature of the surrounding air had no constant effect on the rate of the respiration. In general, however, there was a decided tendency for the rate of the respiration to be lower out of doors than in the ward. There were, nevertheless, many instances in which there was no evident relation whatever between the temperature of the air and the rate of the respiration. In some instances, indeed, the respiration was always more rapid when the child was out of doors.

The impression of the house officers and nurses, who were constantly with the patients, was that, in general, the children were more comfortable out of doors than in the ward. They thought that they coughed less, were quieter, had a better color, and took their food better out of doors than when they were inside. These were, however, merely their impressions, and are, therefore, of little or no scientific value.

The mortality in this series of cases, 25 per cent., was exceptionally high. It shows nothing as to the effect of the cold-air treatment on

the mortality, however, because these patients were not treated consistently either out of doors or in the house. The statistics at present available are, moreover, entirely insufficient to justify any positive conclusions as to what influence the cold-air treatment of pneumonia in children may have upon the mortality. An analysis of all the cases of pneumonia treated at the Children's Hospital since its foundation, made by Cunningham,⁷ shows that the mortality at this hospital has been slightly higher since the introduction of the cold-air treatment than it was before. This fact does not prove at all, however, that the increased mortality was due to the cold-air treatment. It is far more probable that it was caused by the well-recognized increase in the virulence of this disease during recent years.

CONCLUSIONS

The following conclusions seem warranted:

There is no constant relation between the systolic, the diastolic or the pulse pressure and the severity of the pneumonia or the temperature of the surrounding air.

The rates of both the pulse and the respiration show a tendency to vary directly with the temperature of the surrounding air.

The patients symptomatically seem more comfortable when they are out of doors than when they are in the house.

No conclusions are justified as to the effect of the cold-air treatment on the mortality of pneumonia in childhood.

7. Cunningham: *Boston Med. and Surg. Jour.*, 1916, clxxiv, 753.

ACETONE BODY PRODUCTION IN INFANCY AND CHILDHOOD *

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In the course of a number of diseases in infancy and childhood acetone bodies are excreted in the urine in sufficient quantity to be detected by qualitative tests. Acidosis may or may not be present; but in the overwhelming majority of cases with acetonuria acidosis is absent. This statement requires explanation because of the frequent confusion of the two terms, "acetonuria" and "acidosis," which are not synonymous. At one time it was justifiable to consider them so. That was shortly after Stadelmann, Minkowski, Külz and others had shown that the high ammonia coefficient of the urine, which Hallervorden had demonstrated with severe diabetes, was dependent on the presence of beta-oxybutyric acid and its closely associated compound aceto-acetic acid, from which acetone is derived.

As time has gone on, however, it has appeared, first, that a severe disturbance similar to that frequently produced by these acids may be brought about by other substances than beta-oxybutyric and aceto-acetic acids; and, second, that the acetone bodies may appear in the urine, in considerable quantity, in the course of disease or even in starvation, without producing disturbance of any kind. Acidosis has therefore come to mean the disturbance which results from a relative excess of acid radicals in the body, acid radicals of any kind, rather than the detection of one or more of these in the urine by colorimetric tests. The salts of those acids that produce acidosis are not essentially toxic. The acids do harm merely because they are acids and neutralize the bases of the body. Under ordinary circumstances acids that are formed in the body or introduced with the food are neutralized and excreted by the kidneys. But the body has the capacity to neutralize and excrete much more, so that if a moderate amount of acid, such as aceto-acetic or beta-oxybutyric, is formed, it is neutralized and excreted with no important loss of base and there is nothing to indicate an excess of acid formation but an analysis of the urine. There is acetonuria, but no acidosis. If acid is ingested or formed in too great excess or not properly eliminated, the bases of the body are withdrawn

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and the alkali reserve is diminished. There is acidosis, but there is no acetonuria unless the acids in excess are those of the acetone series.

The amount of acid that is ingested and formed and excreted in health is very large; the amount of aceto-acetic acid and its decomposition product, acetone, that is required to give qualitative tests in the urine is insignificantly small, only a fraction of 1 per cent. of the total acid excretion. No impression is made upon the alkali reserve by such an amount. It cannot be denied that under certain circumstances beta-oxybutyric and aceto-acetic acids are produced in quantities sufficient to reduce the alkali reserve; then and only then may acidosis properly be said to be present. This diminution in the alkali reserve is shown clinically by hyperpnea, that is, deep breathing of the air hunger type. In the absence of this, which is not always easy to appreciate in its early stages, laboratory tests of a relatively simple character are required.¹ The diagnosis cannot be made from a qualitative examination of the urine.

The production and excretion of the acetone bodies is not an abnormal process. The amounts present in the urine are usually too small to give colorimetric tests. They may be determined by quantitative methods. Veeder and Johnson² have shown the average daily excretion of the ketones (presumably acetone and aceto-acetic acid) to be 32 mg. and that of beta-oxybutyric acid to be 38 mg. The acetone bodies may also be shown to be present in the blood, as we have frequently demonstrated by a method devised by one of us.³ The amount in health is from 1 to 15 mg. per 100 gm. of blood.

The statement is repeatedly made that the appearance of acetone in the urine indicates a mild metabolic disorder, that aceto-acetic acid is found when the disturbance is greater and that it is only when a serious or dangerous breakdown of the chemical processes occurs that beta-oxybutyric acid is to be found. This is far from the truth. When acetone is present in the urine, and this is the case even in health, aceto-acetic acid is present in considerably larger amount, generally from eight to ten times as much, and beta-oxybutyric acid is present in approximately the same quantity as the aceto-acetic acid. The misconception on this point arises because the nitroprussid test, which is ordinarily used for acetone, is in reality an extraordinarily sensitive test for either acetone or aceto-acetic acid. The ferric chlorid test is a much less delicate one for aceto-acetic acid. The tests for beta-oxybutyric acid are less delicate still. When, therefore, it is said that the nitroprussid test shows acetone and the ferric chlorid test no aceto-

1. Howland and Marriott: *Bull. Johns Hopkins Hosp.*, 1916, xxvii, 65.

2. Veeder and Johnson: *AM. JOUR. DIS. CHILD.*, 1916, xi, 291.

3. Marriott: *Jour. Biol. Chem.*, 1914, xviii, 507.

acetic acid, it means that both are present but only in small amount and that beta-oxybutyric acid is present also.

The preponderance of beta-oxybutyric acid obtains likewise in the blood, for Marriott,⁴ Sassa,⁵ and, recently, Moore⁶ have shown that there is in health usually twice as much or more of this substance than of acetone and aceto-acetic acid combined.

Clinically, we know that acetone bodies are to be found very frequently in the urine of sick children, though we usually do not take the trouble to look for them. Thus, Holt⁷ reported that in 30 per cent. of 200 consecutive cases admitted to the Babies' Hospital the acetone bodies were found in the urine, and that they were present with 70 per cent. of the cases of pneumonia. Frew⁸ found positive tests for the acetone bodies in the urine of more than 60 per cent. of 662 consecutive patients admitted to the Great Ormond Street Hospital. Ludwig Meyer⁹ found a positive Legal's test in the urine of 70 per cent. of patients with diphtheria, of 69 per cent. of those with scarlet fever and of 60 per cent. of those with measles. Acetonuria is certainly common enough with febrile disease, but it is found in many other conditions as well, such as after anesthesia and particularly with partial or complete starvation. Indeed, partial inanition is probably the chief cause. This partial inanition, the result of anorexia in fever or the result of the increased metabolism during the fever, almost inevitably produces acetonuria. If, then, we rely on qualitative urinary tests, such as the nitroprussid and the ferric chlorid, and when they are positive, make diagnosis of acidosis, we can at almost any time and in any place detect an epidemic of acidosis. We reduce the art of diagnosis to the lowest terms and acidosis becomes the most frequent of children's diseases. Acidosis is a frequent condition in infancy and childhood and it is a very important one and very serious, but it is usually not due to the production of the acetone bodies. It is frequent and very fatal with severe diarrhea, as we have shown; it occurs with severe nephritis and with burns, but in such conditions it is not dependent on the acetone bodies. And even when the acetone bodies are to be detected in great quantity, it is necessary, in order to demonstrate that their presence is injurious, to observe hyperpnea or to prove a diminution of the alkali reserve on which the hyperpnea depends. If this is done, here and there a case of acidosis may be detected, but it can confidently be asserted that these cases will not be found in numbers sufficient to announce the occurrence of an epidemic.

4. Marriott: *Jour. Biol. Chem.*, 1913, xvi, 293.

5. Sassa: *Biochem. Ztschr.*, 1914, lix, 362.

6. Moore: *AM. JOUR. DIS. CHILD.*, 1916, xii. Now in press.

7. Holt: *Jour. Am. Med. Assn.*, 1916, lxvi, 144.

8. Frew: *Lancet*, London, 1911, ii, 1264.

9. Meyer: *Jahrb. f. Kinderh.*, 1905, lxi, 438.

The cases that we have studied have been considered rather from the viewpoint of the acetone bodies found in the blood than from the amount eliminated in the urine, since this gives more information in regard to the conditions obtaining at a certain definite time. We have studied the cases also for evidences of acidosis by a number of methods that determine the carbon dioxid tension of the alveolar air and the alkali reserve.

Formerly, diabetes in childhood was accompanied by an enormous increase in acetone body excretion. Death usually took place in coma. With the method of treatment introduced by Allen it is possible to prevent the production of the acetone bodies to such an extent that they may remain, for a long time at least, within normal limits. This we have been able to do with four recent patients, one of whom has been under observation for four years and another for two. The acetonemia of diabetes treated by carbohydrate reduction is frequently not greater than that which we have observed after simple starvation in normal children.

In several cases of ileocolitis there has been found a very marked acetonemia; in one instance the acetone bodies in the blood increased in a day from 16 to 183 mg. per 100 gm. of blood. Another of these children, only 2 years of age, passed more than 8 gm. of these bodies in the urine in twenty-four hours. Acidosis, that is, a diminution in the alkali reserve of the body, was demonstrated in three of the cases. The cause of this excessive production of the acetone bodies is not clear. It far exceeds anything that would result from starvation alone and occurs much more rapidly. These cases are in striking contrast with those of diarrhea of the choleric form type; for in these latter, even when most extreme acidosis is present, the acetonemia is slight. It is often less than in cases of diarrhea without acidosis, and entirely insufficient to be a factor in the disturbance of the acid base equilibrium.

It has long been recognized that acetonuria frequently accompanies vomiting in childhood. Perhaps it is to Marfan¹⁰ that the chief credit is due for emphasizing the regular presence of the acetone bodies in the recurrent, periodic or cyclic type of vomiting. The acetone bodies are so frequently present in recurrent vomiting and often appear so early that tests for their presence are utilized by many in the differential diagnosis of the condition. They have been found even before the vomiting and can often be detected in the urine by qualitative tests at the time of the first vomiting. The chief interest attaches to the mechanism of production of these substances. The most frequent cause of acetonuria is partial or complete starvation. Certainly in many of these cases acetonuria cannot result from starvation, for the

10. Marfan: *Arch. de méd. d. enfants*, 1901, ix, 641.

period of abstinence from food is altogether too short. Nor can the acetonuria be considered comparable to that which occurs in diabetes, for sugar is never found in the urine. Hilliger¹¹ was able to produce attacks of vomiting with acetonuria in one child merely by limiting the ingestion of carbohydrates. When the blood sugar fell to a point somewhat below the normal, that is, 0.07 per cent., vomiting took place. It would seem that the metabolism of the patient whom he studied must have been singularly unusual. Children as a rule will not suffer such a rapid diminution of blood sugar as did his patient, nor will vomiting occur with those subject to recurrent vomiting from the reduction of carbohydrate in the diet for only a few hours. We have found no constant relationship between the sugar content of the blood and the onset of attacks.

More data in regard to the glucose content of the blood in this condition, between and during attacks, are desirable. We are left without an explanation of why there is this rapid and excessive production of the acetone bodies in perhaps the majority of the attacks. It must be recognized that they cannot be held responsible for the vomiting, but rather that they accompany it and that both are better to be considered as evidences of a deep-seated metabolic disturbance, or, as Marfan suggests, of an intoxication analogous to that resulting from the administration of ether or chloroform. It is a metabolic disturbance that leaves no trace, for we cannot consider the insignificant postmortem findings that have been reported in the few fatal cases such as slight hemorrhagic erosions and fatty liver, as satisfactory explanations of death.

Despite the undoubted frequency of this condition, death is very unusual. The great majority of the children do not have acidosis, that is, there is no diminution in their alkali reserve and they recover without alkali therapy. Some may, however, develop acidosis and a very few die apparently from the acidosis. A case of mild acidosis with recurrent vomiting was the following:

A girl of 3½ years began with vomiting, which lasted four days. On the third day there was slight hyperpnea, an appreciable diminution of the alkali reserve,¹² and the acetone bodies in her blood were 84.5 mg. per 100 gm. of blood. By giving sodium bicarbonate her alkali reserve was renewed, and shortly after the cessation of the vomiting she was as well as usual. She has since had other attacks.

A fatal case that we have already reported was briefly as follows:¹

A colored boy 3½ years old began to vomit without apparent cause when on a rational diet. The vomiting was continuous, nothing being retained. His condition rapidly became worse and he was brought to the hospital at the end of forty-eight hours in coma and with hyperpnea. There was a great reduction

11. Hilliger: *Jahrb. f. Kinderh.*, 1914, lxxx, 1.

12. R_pH of the serum, 8.2. See Marriott: *Arch. Int. Med.*, 1916, xvii, 840.

in his alkali reserve and his blood contained the surprising amount of 170 mg. per 100 gm. of blood. This approximates the amount found in diabetic patients with coma. The acetone bodies were quite plainly the cause of the acidosis. He died shortly after admission. The necropsy revealed no satisfactory explanation for death.

This was the boy's first attack of excessive vomiting, but the continuous and severe vomiting without any determinable cause in life or post mortem makes it apparent that it should be included among the cases of vomiting with acetonuria. There are other cases that are not so clear, in which the vomiting is slight or entirely absent and in which the acetonemia dominates the whole picture. Two cases that we have observed were as follows:

(1) A boy of 3 years, with a renal tumor and a metastasis in the antrum of Highmore, vomited two or three times one day, but not thereafter. He complained of a sensation of breathlessness. This gradually increased and thirty-six hours later he was in much distress with marked hyperpnea. There was no cyanosis. All the tests showed acidosis, that is, a distinct diminution in his alkali reserve.¹³ He was given sodium bicarbonate by mouth, by rectum and intravenously. This last method of administration brought about almost instantaneous relief and in forty-eight hours he was quite as he was before the attack. He passed 16 gm. of beta-oxybutyric acid and 4 gm. of aceto-acetic acid in his urine in twenty-four hours. Four weeks later, a similar attack, nearly as severe, occurred without any vomiting. This was also promptly terminated by an intravenous infusion of sodium bicarbonate.

(2) A strong, vigorous infant of 1 year of age, who had been exclusively breast fed, began suddenly with vomiting, which was not long continued. He was irritable and restless and later became drowsy. Three days after the onset hyperpnea was noticed, and four days after this it was intense. He was in stupor with a fever of 101.5 F. All the laboratory tests were conclusive of acidosis.¹⁴ His blood contained 136 mg. of the acetone bodies per 100 gm. He died less than twenty-four hours after admission to the hospital.

The cause of the acetonemia in such cases is as obscure as it is with recurrent vomiting. It certainly does not result from deficiency of carbohydrates in the food. It is perhaps best to look on all of these cases, including those of recurrent vomiting with early and severe acetonemia, as really one condition. The vomiting may, in some cases, be present and continuous, in others it may be slight or entirely absent. The vomiting thus would not be considered an essential feature. Theorizing is permissible, but does not yield much information unless supported by direct observations concerning the chemical processes of intermediary metabolism. It is of importance from the therapeutic point of view to recognize that acetone body acidosis sufficient to cause death may arise spontaneously and without vomiting. Overcoming the acidosis when it is very severe is the essential factor in treatment, for the acetonemia arises rapidly and apparently spontaneously, but the

13. Sellards' test colorless on evaporation; pH of serum, 7.2.

14. Tension alveolar carbon dioxid 20 mm., pH of serum, 7.2, RpH of serum, 7.75.

excessive production of acids ceases also spontaneously and rapidly. It is self-limited and does not depend on chronic disease, even though the attacks may be repeated.

SUMMARY

Acidosis and acetonuria are not synonymous terms.

There is no justification for believing that acidosis due to the acetone bodies occurs in epidemic form.

Deficient food or increased requirement for food (disproportion between caloric intake and output) is the chief cause of acetonuria, but this rarely results in acidosis.

The production of acetone bodies occurs at times when starvation cannot be held responsible. The production is rapid and excessive and sufficient to cause a severe or fatal acidosis. This condition is not necessarily accompanied by vomiting. It probably depends on the same underlying metabolic disturbance as do the majority of cases of recurrent vomiting.

PROVOCATIVE AND PROPHYLACTIC VACCINATION IN THE VAGINITIS OF INFANTS*

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We have had to contend with the problem of vaginitis, just as so many others have had to do in similar institutions. It is not my intention to write a review of the trials and tribulations encountered during the five years since we have been housed in modern buildings and have made every effort to combat this insidious disease. As we have profited in some respects by experience, however, it seemed as if it might be of value to those who are actively interested in this problem to communicate briefly some of the lessons learned during this period.

Our endeavors have been directed in various directions: in preventing the admission of infected infants, in attempting in many different ways to avoid a spread of infection, in diagnosing cases at the earliest possible moment, and, finally, in resorting to every means to effect a cure. It should be realized at the outset, although the distinction is not always sharply drawn, that vaginitis presents a problem in a home or asylum for infants totally different from that which it presents in a hospital. In the latter the solution is comparatively simple, for all that is necessary in order to eradicate the disease is to cease admitting girl infants and to discharge those infected, one by one, as they are cured of the ailment for which they were admitted to the hospital. In the asylum, on the other hand, when a case of vaginitis slips past the admitting physician, or arises apparently *de novo* in one of its wards, it is realized that a heavy burden has fallen on the medical staff, for this infant will have to be guarded under quarantine for months or years, and will at all times constitute a threatening source of infection. We have had a variable degree of vaginitis; at times a lull, at others a sudden increase in numbers. At present, due to the regulations which are in force, the number of cases is comparatively few. It may be remarked, however, that during these years no instance of ophthalmia, of arthritis, or of infection of any of the personnel has occurred. There have been four instances of specific urethritis in boy infants, and one of rectal infection. This urethritis lasted but a few weeks and

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did not give rise to a positive complement fixation reaction, so that we believe it involved merely the anterior urethra.

The diagnosis of gonococcus vaginitis is not always easy to establish. In the first place, it is at times confused with other types of this disease, for there is no doubt that this inflammation may be due to micro-organisms other than the gonococcus. For months we harbored a case due to the streptococcus, which was present in almost pure culture in the vaginal discharge, and was furthermore identified on postmortem examination from cultures taken from the cervical canal. There was an absence of gonococci both during life and after death. These, however, are not the difficult instances we refer to, but the borderline cases, which are exceedingly puzzling, especially those showing merely pus cells on microscopic examination. If these cells are numerous, an inflammation is undoubtedly present, and in the great majority of cases the infecting organism will prove to be gonococcus. The specific nature of this infection is all the more probable if there are no micro-organisms to be seen in the field among the cells. One exception should be borne in mind as to the diagnostic significance of pus cells. This subject was called to our attention by noting many leukocytes in the smear of an infant only 48 hours old, who was brought to the institution for admission. It hardly seemed as if this were an instance of gonococcus vaginitis, although it is perfectly possible for an infant to be infected in this way during parturition, so we had some tests carried out in order to ascertain how often pus cells are encountered in smears taken from infants during the first two days of life. These tests were kindly carried out by Dr. Edwin Langrock. They showed that in about 50 per cent. of infants pus cells may be found in vaginal smears taken within the first forty-eight hours of life, so that it would seem that they must not be regarded as pathologic, but probably as the reaction of the external tissues to the inevitable invasion by bacteria. Possibly a similar inflammatory reaction occurs in the intestinal canal.¹ It should be understood that for these vaginal smears, as well as all others referred to in this paper, an applicator tipped with moistened cotton was inserted deep into the vagina, so as to come in contact with the cervix.

As we inquire deeper into the cause of the spread of vaginitis, it would seem to resolve itself, in the last analysis, to a consideration of but one more phase of the general problem of the dangerous but healthy carrier. Although there can be no doubt that the disease is frequently communicated by means of clothing or utensils, the fundamental cause of the infection of one or more infants, in institutions where every

1. In this connection it would seem of interest to note that leukocyte counts of new-born infants were found frequently to be high, the total per cubic centimeter reaching from 15,000 to 23,000, with a differential cell count representing the adult type, namely, from 60 to 75 per cent. of polymorphonuclears.

care is exercised, must be considered the latent carrier, some healthy infant who harbors the gonococcus. Such has been our experience. For two years a pathologist devoted about two hours daily to the making of routine microscopic examinations of vaginal smears of the infants in the asylum. Wherever a case of vaginitis arose, the routine procedure was to make examinations three times during the following week on every infant in the ward in order to ferret out the source of the infection. A card catalogue was kept both of the individual infants and the various wards. Repeated tests brought to light some case in which, in spite of the absence of discharge, gonococci were evident in the smears. Recrudescences of infection occurred in one ward or another every few months and sometimes oftener. We are confronted, therefore, with a problem similar to that in typhoid or diphtheria, in which the carrier constitutes the main stumbling block in the path of prophylaxis. In the case of vaginitis the solution is rendered still more difficult in view of the heightened susceptibility of infants to infection.

During the past five years necropsies have been performed on four infants who had vaginitis while in the institution. (We are able to carry out postmortem examinations on fully 75 per cent. of the children who die.) This offered an exceptional opportunity to gain an insight into the pathologic changes of the common nonvirulent form of this infection. The pathology of this disease is generally glossed over in textbook descriptions. Furthermore, judging from the literature, we conclude the number of postmortem examinations of cases of this type is not large. We should expect this to be the case, as very few hospitals admit vaginitis, which must therefore constitute merely a chance pathologic condition met with in the course of some primary fatal disease. One of our cases had existed but three weeks, two patients were known to have had vaginitis for months, and one for a year or more. They all showed the same pathologic condition, which may be summarized in a few lines: Macroscopically the vagina appeared negative, as did the body of the uterus and the appendages. The only abnormal condition was redness of the tip of the cervix, which, however, did not extend along the canal to the internal os. Microscopic examination confirmed the gross anatomic appearance of these structures. In every instance the entire vagina, the uterus and the tubes were removed for microscopic examination, which was kindly carried out by Drs. Eli Moschowitz and Alwin Pappenheimer, whom I take pleasure in thanking for their courtesy in this connection. The sole lesion was an inflammation of the cervix about the external os, a round-cell infiltration of the submucous tissues. Guided by these postmortem examinations, we must regard, it would seem, the average gonococcus infection as involving the cervix rather than the vagina, and must consider the infection a cervicitis rather than a vaginitis. It

is in the cervix that the gonococcus finds a most favorable nidus. In a study published a few years ago from this service by Rubin and Leopold,² an inflammation of the cervix was frequently seen by direct examination. In the recent preliminary report of the vaginitis committee of the American Pediatric Society³ it may be noted that eleven gynecologists who responded to their questionnaire thought that the cervix or uterus at times showed evidences of this disease. In the adults it has been reported that 95 per cent. of the chronic cases showed a cervicitis.⁴ As the result of personal experience we must conclude that the vagina is comparatively immune in this infection, especially when the disease has reached the subacute or chronic stage.

There seems to exist a very general impression that vaginitis is more particularly a disease associated with child-caring institutions, and that infants brought up in the homes of the poor are infected far less frequently. This has not been our experience. During the year 1915 sixty-six infant girls were admitted to the institution and seventy-two rejected; of these seventy-two, sixty were refused admission on account of vaginitis, thus making the total infection noted in these children almost 50 per cent. It should be added that only three of the rejected patients were referred from other institutions, and that the remainder came direct from their homes. Further investigation may possibly show that this ratio of positive cases is exceptionally high. As a result of having to refuse so many infant girls the institution now harbors one-third girls and two-thirds boys. It would be of theoretical as well as of great practical interest if we could know the results of a similar examination of older girls. From a limited experience of girls between the ages of 4 and 10 at the Tuberculosis Preventorium, I may state that not a few children of this age show signs of infection, although the danger of the spread of the disease seems to have become greatly lessened at this age.

One of the great difficulties in trying to combat vaginitis or cervicitis is that we find it impossible to recognize the infectious case in its earliest stage, in other words, the danger of the latent carrier. To overcome this difficulty we have made many attempts to convert the carrier into an open or florid case. Various drugs have been injected into the vagina in order to bring this about, but as they were found of no practical value, it would serve no purpose to enter into detail concerning efforts of this kind. For the past year, with this end in view, all infant girls have received three subcutaneous injections of gonococcus vaccine soon after they were admitted to the institution. These infants, it should be understood, had all shown an absence of pus cells on admission. The vaccine was prepared from a culture isolated

2. Rubin, I. C., and Leopold, J. S.: *AM. JOUR. DIS. CHILD.*, 1913, v, 58.

3. *Tr. Am. Ped. Soc.*, 1915, xxvii, 331.

4. Menge, K.: *Handbuch der Geschlechtskunde*, Vienna, 1912, ii, 323.

from one of the cases in the institution, and 250, 500, and 750 millions were injected with three day intervals. The object of these vaccinations was to determine whether they would prove provocative and bring to light latent infections. In adults with urethritis it has been found by Asch⁵ that injections of vaccine lead to a discharge containing pus cells and gonococci. The dosage which we used was entirely empirical. As a result of experience it would seem that it could be much smaller; indeed, at the present time we are giving only 100, 200 and 400 millions. Moreover, two injections may prove sufficient, as we have rarely brought about a discharge by means of a third inoculation. During the past year such provocative injections have led to the discovery of eight new cases during the first week or two following their admission (Table 1), and to the unprecedented result that not one case of vaginitis has slipped into the main institution from the admitting pavilion. We have made use of this diagnostic aid not only at the time of admission, but in order to discover carriers in dormitories, where sometimes sporadic cases of vaginitis arose (Table 2). For example, in one ward of twelve infants in which the girls had been free from vaginitis for a period of six to eighteen months, an active case suddenly developed, and although cervical smears failed to disclose its source, two carriers were brought to light by means of provocative inoculations. This has been the case on other occasions. This spring one case of vaginitis with gonococci and another showing pus cells, but no micro-organisms, was unexpectedly and unaccountably noted in the infirmary. There were six infant girls at the time in this ward. Provocative inoculation disclosed four positive cases after a second inoculation. Here was a veritable latent epidemic, which was uncloaked by means of the vaccine.

We are unable to state the exact scientific basis of the reaction following these inoculations. It is, however, not due to a rise of temperature. This was evident, as it occurred to a marked extent in some instances in which there was no febrile reaction whatsoever. It cannot be regarded as absolutely specific, for a positive result was brought about at times by similar injections of staphylococcus vaccine, although this was not found to be so reliable for this purpose as that made from the gonococcus. Indeed it is becoming more and more evident that many similar reactions of the tissues which we have been wont to regard as specific in nature, must be considered in large measure systemic cellular reactions. Whatever may prove to be its exact scientific basis, we firmly believe that it will be found of great practical aid in combating this difficult infection. The same principle might perhaps be applied to facilitate the recognition of carriers in other infections, for example, typhoid fever and pyelitis.

5. Asch, P.: München. med Wchnschr., 1915, No. 39.

TABLE 1.—ROUTINE PROVOCATIVE VACCINATIONS

Name	Age	Admitted	Date of Vaccination	Cervical Smear	Vaginal Discharge	Macroscopic Pus	Microscopic Pus	Gonococci	Remarks
M. G.	8 mo.	11/15/14	11/15/14	—	—	—	—	Date of vaccination is always that of the first injection; two other injections were given at three day intervals
				12/12/14	—	+	+	—	
			4/27/15	4/25/15	+	+	+	—	
				5/ 1/15	+	+	+++	+	
				5/ 3/15	+	+	+++	+	
A. S.	11 mo.	4/15/15	4/15/15	—	—	—	—	Smear after third injection loaded with gonococci; discovered in reception pavilion
				4/20/15	—	—	—	—	
			4/24/15	5/ 6/15	+	+	+	+	
				6/ 1/15	+	+	+	+	
				7/10/15	+	+	+	+	
H. B.	3 mo.	12/21/15	12/21/15	—	—	—	—	Vaccine given a second time to discover latent infection in this ward
			2/ 2/16	2/ 9/16	—	—	—	—	
				2/25/16	—	—	++	—	
			3/ 1/16	3/16/16	—	+	++	—	
				3/29/16	—	+	++	+	
R. G.	11 mo.	12/14/14	12/14/14	—	—	—	—	Vaccinated in order to find gonococci; a discharge resulted which lasted about a month and a half
				1/ 9/15	—	+	—	—	
				3/ 1/15	—	+	++	—	
			4/27/15	5/ 5/15	+	+	+	+	
				6/ 1/15	+	+	+	+	
E. S.	3 yr.	11/ 1/15	11/ 1/15	—	—	—	—	Vaginal discharge incited, which lasted about three weeks
			11/21/15	11/29/15	+	+	+	+	
				12/16/15	+	+	+	+	
				3/ 7/16	—	—	—	—	
				3/10/16	—	+	+	+	
M. H.	3 yr.	7/13/15	7/13/15	—	—	—	—	Vaginal discharge incited, which lasted about two weeks; discovered in reception pavilion
			7/15/15	7/29/15	+	+	+	+	
				8/ 3/15	—	±	+	+	
				8/ 9/15	—	—	—	—	
				3/10/16	—	+	+	—	
				4/14/16	—	—	+		

TABLE 2.—PROVOCATIVE VACCINATION IN OLD CASES OF
VAGINITIS, LATENT CARRIERS

Name	Date of Vaccination	Cervical Smear	Vaginal Discharge	Macroscopic Pus	Microscopic Pus	Gonococci	Remarks
S. L.	1/15/14	+	+	+	—	Positive result after negative period of two years
		12/20/15	—	—	—	—	
		12/30/15	—	—	—	—	
	2/ 1/16	2/ 6/16	—	—	+++	—	
		2/ 9/16	—	—	++	+	
		4/20/16	—	—	+	—	
F. G.	11/ 8/14	—	+	—	—	No temperature reaction
		12/20/14	—	+	+	—	
		12/20/15	—	—	+	—	
		12/30/15	—	—	—	—	
	2/ 1/16	2/ 6/16	—	—	+	—	
		2/ 9/16	—	—	+	—	
		4/20/16	—	—	+++	++	
L. E.	5/ 7/16	—	—	+	—	No temperature reaction
		11/ 8/14	—	+	+	—	
		12/20/14	—	+	++	—	
		12/20/15	—	—	+	—	
	2/ 1/16	12/30/15	—	—	+	—	
		2/ 6/16	—	—	++	—	
		2/ 9/16	—	—	+++	+	
G. S.	4/20/16	—	—	—	—	
		11/10/14	—	+	+	+	
		12/ 8/14	—	+	++	—	
		1/20/15	—	+	+	—	
	2/ 1/16	12/15/15	—	—	—	—	
		12/30/15	—	—	—	—	
		2/ 6/16	—	—	+++	+	
F. G.	2/ 9/16	—	—	++	+	
		4/20/16	—	—	—	—	
		6/ 8/14	+	+	+	+	
		12/15/14	—	+	+	—	
	2/ 1/16	1/12/15	+	+	+	—	
		12/20/15	—	—	—	—	
		12/30/15	—	—	++	—	
	2/ 1/16	2/ 6/16	—	—	++	—	
		2/ 9/16	—	—	++	+	
		4/20/16	—	—	+	+	

TABLE 2.—PROVOCATIVE VACCINATION IN OLD CASES OF VAGINITIS, LATENT CARRIERS—(Continued)

Name	Date of Vaccination	Cervical Smear	Vaginal Discharge	Macroscopic Pus	Microscopic Pus	Gonococci	Remarks
R. L.	5/18/14	—	+	++	—	Went home in April
		12/20/14	—	+	+	—	
		12/18/15	—	—	—	—	
		12/30/15	—	—	—	—	
	2/ 1/16	2/ 8/16	—	—	++	—	
		2/ 9/16	—	—	++	+	
S. R.	10/12/14	—	+	—	—	
		12/15/14	—	+	+++	—	
		1/18/15	+	+	+	—	
		12/20/15	—	—	—	—	
		12/30/15	—	—	+	—	
	2/ 1/16	2/ 6/16	—	—	++	—	
B. K.	12/10/14	—	+	—	—	
		1/12/15	—	+	—	—	
		12/20/15	—	—	—	—	
		12/30/15	—	—	+	—	
	2/ 1/16	2/ 6/16	—	—	+	—	
		2/ 7/16	—	—	++	+	
		4/30/16	—	—	+	—	

The vaccine was found to be of value not only as a diagnostic, but, to a certain extent, as a prophylactic measure. To this end we used it on about seventy-five infants and were able to change the entire nature of vaginitis in our institution. In patients who were vaccinated the vaginitis showed a mild type of infection. It is not to be expected that prophylactic injections can prevent the occurrence of carriers, just as diphtheria antitoxin cannot obviate the occurrence of diphtheria carriers, and typhoid vaccine cannot prevent the implantation of typhoid bacilli in the mucous membrane. However, the protected patients, instead of developing a vaginal discharge full of pus cells and gonococci, were found to have no discharge whatsoever, and to show as the only evidence of infection a few pus cells and microorganisms in the cervical smears. In other words, a nonclinical type of disease resulted. The bacteria frequently appear atypical under these conditions; they are degenerated and often very small, as has been described by many in connection with chronic cases. It is too early to state how long this partial immunity will last. We have not

attempted to control its course by means of complement fixation, as our experience with this reaction has not been entirely satisfactory. For three years we made serum tests of this kind on the infants in the institution, in order to judge of the persistence of infection, but the results proved so contradictory that the attempt to solve the question by this means was abandoned.

There are some diseases which occasion not only a recrudescence of vaginitis, but seem to confer a susceptibility to infection. This is especially true of scarlet fever. In this disease the susceptibility extends still farther, in that a systemic lack of resistance to the gonococcus results, so that joint infections and other evidences of a specific bacterial invasion result. Recently Nicoll⁶ reported three cases of gonococcus arthritis in children from the scarlet fever pavilion of the Willard Parker Hospital, and others have been noted in these wards from time to time. However, there is not merely an acquired susceptibility and probably also a natural susceptibility to gonococcus infection, but also a well defined natural immunity. This has been very evident in individual instances among the infants in the asylum.

At times it has been very difficult to carry out an absolute isolation of vaginitis patients, more especially when some infectious disease has visited the institution. For example, about two years ago, during a considerable epidemic of whooping cough, it became necessary to isolate the children according to the presence of pertussis rather than according to vaginitis. Under such conditions it was observed that some infants did not develop vaginitis in spite of some months of exposure in these wards. In other words, these babies possessed a high degree of immunity (Table 3). Since then this idiosyncrasy has been confirmed by further observations and there are at present five, or possibly six, infants in the institution who may be said to be immune, or almost immune, to this infection, and who during the past two years several times have chanced to be in wards in which vaginitis broke out and who nevertheless each time have escaped infection. These cases have been given provocative vaccination in order to make certain of their freedom from infection, but in every instance this has failed to incite any inflammatory reaction. We do not know whether this is to be considered a local or systemic immunity. We may, however, call attention to the fact that there seems to be no doubt that a similar immunity exists in the adult. It is to be remembered in this connection that there is frequently a difference in the configuration of the epithelium in different individuals. In some, the columnar epithelium begins outside of the cervix, in others the squamous epithelium, which is typical of the vagina, extends even into the cervical canal. These variations, as well as others relating to the number, the size, and the patency of the

6. Nicoll, M.: *Arch. Pediat.*, 1914, No. 11, 804.

TABLE 3.—CASES OF NATURAL IMMUNITY *

Name	Admitted	Age on Admission	Cervical Smear	Vaginal Discharge	Macroscopic Pus	Microscopic Pus	Gonococci	Provocative Vaccination
P. K.	5/29/12	6 mo.	6/24/14	—	+	—	—	7/15/15
			8/16/14	—	—	—	—	
			9/15/14	—	+	—	—	
			12/30/14	—	+	—	—	
			7/ 8/15	—	—	—	—	
			7/15/15	—	—	—	—	
			7/20/15	—	—	—	—	
			3/ 7/16	—	—	—	—	
			5/ 4/16	—	—	—	—	
R. C.	5/23/13	2 yr.	5/24/14	—	+	—	—	7/15/15
			5/26/14	—	—	—	—	
			6/24/14	—	+	+	—	
			1/ 5/15	—	—	—	—	
			5/14/15	—	+	—	—	
			7/ 9/15	—	+	+	—	
			7/20/15	—	+	+	—	
			9/15/15	—	—	+	—	
			12/30/15	—	+	—	—	
N. S.	4/21/14	3 yr.	2/24/16	—	+	—	—	7/15/15
			3/ 6/16	—	—	—	—	
			7/25/14	—	—	—	—	
			7/ 8/15	—	—	—	—	
			7/10/15	—	—	—	—	
			7/20/15	—	—	—	—	
			9/ 7/15	—	—	+	—	
			12/30/15	—	+	—	—	
			2/ 6/16	—	+	++	—	
F. B.	6/16/12	2 yr.	3/ 4/16	—	—	+	—	7/15/15
			5/ 4/16	—	—	+	—	
			6/24/14	—	+	—	—	
			7/10/15	—	—	—	—	
			7/20/15	—	—	—	—	
			9/ 7/15	—	—	+	—	
			12/30/15	—	+	+	—	
			3/ 4/16	—	—	—	—	

* Unavoidably exposed for some months during spring of 1914, due to pertussis epidemic.

cervical glands, have been shown to be present in earliest infancy.⁷ As is well known, the gonococcus has a particular affinity for surfaces covered with columnar epithelium, and is not able to attack those lined with squamous cells. This immunity is rare. In many instances it is probably not absolute and sooner or later, in the course of months, it will be found that infection takes place. It is reported as an observation of interest, rather than as one which can play a rôle in the epidemiology of this disease.

CONCLUSIONS

Postmortem examinations show that in the subacute and chronic cases of vaginitis in infants the cervix is most frequently involved and that the vagina generally shows no signs of inflammation. Cervicitis would therefore seem to be a more correct term, in this connection, than vaginitis.

Where numerous pus cells without bacteria are found in smears made from the cervix, an inflammation may be assumed to be present, and in the overwhelming majority of instances the inciting factor will be found to be the gonococcus. Other micro-organisms may, however, be the cause of the inflammatory process, for example a streptococcus, as in a case which was studied both during life and after death. It should be borne in mind that smears taken from new-born infants very frequently show pus cells, probably due to the invasion of the vagina by saprophytic bacteria, and that, in the new-born, they should not be considered pathologic or as evidence of gonococcal inflammation.

Gonorrheal vaginitis, or cervicitis, should not be regarded as a disease encountered especially in institutions, as it may be found in a considerable proportion of infants living in the crowded tenements in the city.

In child-caring institutions the greatest obstacle to limiting and controlling the spread of this disease is the difficulty of recognizing latent cases. It affords, therefore, but one more aspect of the problem of the healthy but dangerous carrier, and of the difficulty of devising methods to prevent contact infection. By means of provocative inoculations of gonococcus vaccine we have found it possible to convert the concealed carrier into an open case, and in this way to discover many cases which had eluded detection. Vaccinations have also some prophylactic value, and may either confer protection or render subsequent infection of a mild character, so that it assumes a bacteriologic rather than a clinical type.

There is not only a natural susceptibility to this infection and an acquired susceptibility, as occurs in the course of scarlet fever, but a natural immunity, which may be sufficient to protect infants who come in contact with infected patients.

16 West Eighty-Sixth Street.

7. Moericke, R.: *Ztschr. f. Geburtsh. u. Gynäk.*, 1882, vii, 84.

PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE OF THE PAST TWO YEARS ON THE ORGANS OF INTERNAL SECRETION

EDWARDS A. PARK, M.D.

BALTIMORE

The review which follows is intended to cover those parts of the literature on internal secretions of the past two years which have seemed to the writer to be especially important or interesting. It was found impossible to master the entire literature that has sprung up about this fruitful subject, much less to include it in its entirety in a review, so that some important work may receive no mention. Certain organs known to have an internal secretion, the genital glands and pancreas, and others thought by some to possess an internal secretory function, such as the kidney, have been purposely omitted from consideration for lack of time and space for adequate treatment. On the other hand, the pineal and carotid glands, which have been much exploited recently, have been discussed in some detail, although no certainty exists that they are organs of internal secretion. Pende's "new organ of internal secretion" has been included.

The citations of the literature are not absolutely complete. Certain references which seemed to be of little value have been purposely omitted from the list, and doubtless some important references have been accidentally passed over.

THE SUPRARENALS

Thomas,¹ and Elliott and Armour,² both writing in 1911, described the histologic changes which occur in the cortex of the suprarenal shortly after birth. It is well known that the suprarenal of the newborn child is considerably larger, relatively speaking, than the suprarenal at a later period of childhood or in adult life. At the third post-natal month it actually weighs less than at birth (Elliott and Armour), although the body weight has increased by one half or two thirds. According to Elliott and Armour the cortex of the suprarenal at birth is composed of a narrow outer rim of cells, from which develops

1. Thomas, E.: Beitr. z. path. Anat. u. z. allg. Path., L, 283; cited by Pappenheimer.

2. Elliott, T. R., and Armour, R. G.: Jour. Path. and Bacteriol., 15, 1911.

the adult cortex, and between this rim and the medulla an enormous mass of fetal cortex, destined almost immediately to disappear. The medulla at birth is a thin core, not much more than a line in thickness, which increases in size progressively as age advances. The largest part of the chromaffin tissue of the new-born child lies outside the suprarenals in the paraganglia of the sympathetic. But these paraganglia dwindle as the medulla of the suprarenal increases. "Generalizing roughly, one may say that the fetal cortex, which was so large, and the fetal paraganglia perish and are replaced by a new cortex and a new medulla, which constitutes the adult gland" (Elliott and Armour). The fetal portion of the cortex of the suprarenal contains at birth blood vessels, but not the lipid substance, which seems to be the characteristic product of the permanent cortex. Immediately after birth it undergoes fatty degeneration and vanishes, but the outer rim, which contains the characteristic lipid even before birth, increases in size and forms the permanent cortex of the gland.

Lewis and Pappenheimer³ have studied the suprarenal gland in a large series of children dying within the first three weeks of life. According to them the degenerative changes appear in the cortex very soon after birth, and are practically complete by the end of the second week. They cause an abrupt diminution in the breadth of the cortex. No regenerative process can be detected during the first three weeks of life. They think the fibrous tissue which in the mature gland separates the medulla from the cortex is formed simply by the collapse of the connective tissue framework of the fetal portion of the cortex as the result of the degeneration and disappearance of its parenchymatous cells. Neither prematurity nor inanition modify the course of the involution.

Kern, who has looked for these changes in the suprarenals of pigs, rabbits, calves, sheep, rats and horses, has been unable to find them. If his observations are correct, the process seems to be peculiar to human beings. Elliott and Armour also state that the suprarenals of animals (they have not examined the suprarenals of the monkey) are smallest at birth and increase in size progressively as age advances, a fact which speaks against the occurrence in the suprarenals of animals of the cortical changes in man.

The active principle of the suprarenal (epinephrin) McCord demonstrated in very young beef fetuses by means of the uterus strip method.

3. Lewis, R. W., and Pappenheimer, A. M.: A Study of the Involutional Changes Which Occur in the Adrenal Cortex During Infancy, *Jour. Med. Research*, 1916, xxxiv, 81.

J. H. Lewis⁴ on the other hand, failed to detect epinephrin in the suprarenals of human fetuses, even at term; and Elliott could discover only a trace of the epinephrin in the suprarenals of new-born children, although he found definite evidence of epinephrin in the paraganglion aorticum, a mass of chromaffin tissue situated close to the suprarenals. The epinephrin content of this ganglion was 1/500 of its weight. Similar negative results in human beings have been reported by Moore and Purinton,⁵ 1900, and Svehla,⁶ 1900, using the older, less accurate chemical methods. The method which Lewis employed for the detection of epinephrin was the chemical method advocated by Folin, Cannon and Denis.⁷

Cannata⁸ could find no epinephrin in the blood of new-born children—an experimental result to be anticipated.

Fulk and Macleod⁹ report that acid extracts of retroperitoneal chromaffin tissue of man, the dog, cat, rabbit, guinea-pig, white rat, calf, sheep and pig have the same physiologic action on excised strips of intestine and uterus as the active principle of the medulla of the suprarenal gland.

Stewart, Rogoff and Gibson¹⁰ have been able to detect epinephrin in the blood after stimulation of the peripheral end of the splanchnic nerve, according to the method of Joseph and Meltzer. These last-named investigators found that when one cervical ganglion was removed in the rabbit and several days later the peripheral end of the splanchnic nerve stimulated, there occurred an unmistakable dilation of the pupil on the ganglion-free side. Removal of the ganglion of the sympathetic had rendered the pupil on that side far more sensitive to epinephrin. Stewart, Rogoff and Gibson found that this characteristic response was obtained when epinephrin was injected into the blood stream and was not obtained when the splanchnic was stimulated after the suprarenals had been removed, or when the circulation was interfered with in such a way that epinephrin could not reach the eye. The latent period for liberation of epinephrin from the suprarenals

4. Lewis, J. H.: Presence of Epinephrin in Human Fetal Adrenals, *Jour. Biol. Chem.*, 1916, xxiv, 249.

5. Moore, B., and Purinton, C. O.: *Am. Jour. Physiol.*, 1900, iv, 57; cited by Lewis.

6. Svehla: *Arch. f. exper. Path. u. Pharmacol.*, xliii, 321; cited by Lewis.

7. Folin, Cannon and Denis: *Jour. Biol. Chem.*, 1912-1913, xiii, 477; cited by Lewis.

8. Cannata, S.: Sulla presenza di adrenalina, nel sangue del neonato, *Pediatria*, 1915, Series 2, xxiii, 244.

9. Fulk, M. E., and Macleod, J. J. R.: Evidence That the Active Principle of the Retroperitoneal Chromophil Tissue Has the Same Physiological Action as the Active Principle of the Suprarenal Glands. *Am. Jour. Physiol.*, 1916, xl, 21.

10. Stewart, G. N., Rogoff, J. M., and Gibson, F. S.: The Liberation of Epinephrin from the Adrenal Glands by Stimulation of the Splenic Nerves and by Massage, *Jour. Pharmacol. and Exper. Therap.*, 1916, viii, 205.

was exceedingly short, since the eye response seemed to occur at the same interval (a fraction of a second) whether the splanchnic nerve was stimulated or epinephrin injected into the renal vein. Massage of the suprarenal produced a similar eye response to that obtained by splanchnic stimulation. It was not found possible to exhaust the epinephrin supply in the suprarenals by fright, or morphin administration to such an extent that the characteristic effect on the eye could not be produced by splanchnic stimulation.

Hartmann¹¹ found that dilute solutions of epinephrin, for example, 1 to 100,000, caused a fall in blood pressure in the peripheral vessels, even after the latter had undergone dilatation as a result of hemorrhage, but that the same concentration of epinephrin produced a constriction of the splanchnic vessels.

Other investigators have previously reported dual action of epinephrin in dilute as compared with stronger concentration. Brodie and Cullis,¹² for example, found that minute concentrations produced constriction of the coronaries of animals, while stronger concentrations caused dilatation.

Hoskins¹³ has conducted feeding experiments on white rats with desiccated suprarenal gland. The animals numbered forty-five, twenty-six serving as controls. Controls and experimental rats were of the same litters. The feedings were kept up from two to nine weeks. Hoskins found that the testes of the suprarenal fed animals showed definite hypertrophy, in accordance with the clinical evidence that the suprarenal cortex exerts a stimulating influence on the growth of the testes. No other effects of the suprarenal feeding were found. There were no disturbances in the growth or development of the rats.

Stilling,¹⁴ in 1888, discovered that when one suprarenal is removed, the remaining gland undergoes compensatory hypertrophy and that it is the cortical and not the medullary portion which is affected. Biedl¹⁵ in 1899 demonstrated by extirpation experiments in fish that the cortical and not the medullary element is essential to life. Crowe and Wislocki¹⁶ have now found that after partial extirpation of the suprarenal, the part of the cortex which is left undergoes hyper-

11. Hartman, F. A.: The Differential Effects of Adrenin on Splanchnic and Peripheral Arteries, *Am. Jour. Physiol.*, 1915, xxxviii, 438.

12. Brodie and Cullis: *Jour. Physiol.*, 1911-1912, xliii, 313.

13. Hoskins, R. G.: The Effects of Suprarenal Feeding, *Arch. Int. Med.*, 1916, xvii, 584.

14. Stilling, H.: *Rev. de Méd.*, 1888, T9, 459; cited by Crowe and Wislocki.

15. Biedl, A.: *Innere Sekretion, ihre physiologischen Grundlagen und ihre Bedeutung für die Pathologie*, 1913.

16. Crowe, S. J., and Wislocki, G. B.: Experimental Observations on the Suprarenal Glands with Especial Reference to the Functions of Their Interrenal Portions, *Bull. Johns Hopkins Hosp.*, 1914, xxv, 287.

trophy, chiefly in the fascicular zone, while the medullary portion shows no change, either gross or microscopical. After almost total removal of both suprarenals, the animals developed subnormal temperature, frequent convulsions, and entered into a condition analogous to shock. If recovery occurred, it was gradual, but ultimately became complete. Although they found that an autoplasmic transplant of suprarenal might take, the cortical cells surviving while the medullary cells died, such a transplant appeared to have no functional value. The authors had one dog under observation for a year after reduction of the suprarenals to a minute rest, which promptly died with the symptoms mentioned when this rest was removed. The following experiment is particularly instructive. On Nov. 13, 1912, Crowe and Wislicki removed from a dog nine-tenths of the right and one week later the entire left suprarenal. The dog survived. Six months later they ligated the vessels supplying the small piece of the right suprarenal which had been left. The ligation was followed by convulsions, subnormal temperature, etc. The animal surviving, on May 14, 1913, one-third of the rest was removed. Death then occurred in twenty-four hours after characteristic symptoms. The hypertrophy of the cortical portion of the rest was extreme, while the medullary portion showed no hypertrophy.

Elliott¹⁷ has made an extensive study of human suprarenals in health and disease. Among the numerous observations which he has made the following are of particular interest: The lipoids of the suprarenal, which are normally found in the cortex, are stored and consumed under conditions entirely different from those which govern the storage and consumption of the body fat; for example, while the body fat disappears in starvation, the cortical lipoid of the suprarenal persists. The cortical lipoid vanishes rapidly, however, during acute infections and is diminished in chronic infections and anemias. The lipoid content of the cortex and the epinephrin content of the medulla have no relation whatsoever to each other. Elliott suggests that the function of the cortex may be to maintain the cholesterin ester content of the blood, which it is known becomes diminished under the same conditions as those under which the cortical lipoid of the suprarenal becomes diminished. He suggests also that the cortex of the suprarenal has a relationship to growth and sexual maturation. He points out the interesting fact that, morphologically, the cortical cells of the suprarenal are akin to the interstitial cells of the testis.

Turning to the consideration of the medullary function of the suprarenal, he finds no evidence that high blood pressure depends on an increased epinephrin secretion. The epinephrin content is at its

17. Elliott, T. R.: Pathological Changes in the Adrenal Glands, *Quart. Jour. Med.*, 1914-1915, viii, 47.

lowest "in the afebrile acute cardiac failure associated with mental distress in the struggle to live," but is not lower or higher in diseases accompanied by high blood pressure than in others.

Jump, Beates and Babcock¹⁸ have collected from the literature seventeen cases of precocious sexual development associated with suprarenal tumor, all of which were confirmed by necropsy. It is interesting to note that fourteen of the seventeen patients were girls. In all the cases there was an overgrowth of pubic hair; in fourteen of them hair was present on the face; and in five there was axillary hair. Overgrowth of the body as a whole occurred in all. Precocious menstruation and breast development appeared in only one. The majority of the children showed diminished intelligence, but some appeared to be unusually bright. There seemed to be a tendency toward the assumption of the masculine type of sexual development in all the females and an exaggeration of the normal in the sexual development of the males. The tumor always involved the suprarenal cortex.

Baldwin¹⁹ adds another case, a boy 5 years old, whose face was like that of a man and had been shaved for some time. The father thought that the premature sexual development had been evident at about the 18th month. Hair on the pubis and face appeared at 3, and at that time it was noticed the voice was like that of a man. The genitalia resembled those of the adult, except that the testes were small and not completely descended. Necropsy showed a large hypernephroma of one suprarenal and a small one of the other. The other organs of internal secretion were normal.

Van der Bergh reports still another case of hypernephroma of the suprarenal in a girl of 3 years with somatic changes analogous to those just described. The girl was from 4 to 5 inches taller than the average, and her general aspect and the appearance of her genital organs suggested the adult state. There was no indication of pineal or hypophysial tumor. The hypernephroma was removed and weighed 2,000 gm. Van der Bergh reviews the literature. The ages in his group of cases ranged from 14 months to 14 years; two girls of 5 and 9 years had beards; extreme obesity occurred in several cases.

THE CAROTID "GLAND"²⁰

Luschka, in 1862, gave the first accurate histologic description of the carotid bodies and expressed the view that they were glands and

18. Jump, H. D., Beates, H., Jr., and Babcock, W. W.: Precocious Development of the External Genitals Due to Hypernephroma of the Adrenal Cortex, *Am. Jour. Med. Sc.*, 1914, cxlvii, 568.

19. Baldwin, J. F.: Adrenal Precocity; Precocious Development of the External Genitals Due to Hypernephroma of the Adrenal Cortex, *Jour. Am. Med. Assn.*, 1914, lxiii, 2286.

20. Betke's article, on which this review is based, contains a complete bibliography and discussion of the entire subject.

not nervous tissue. Arnold, on the other hand, considered them actually to be blood vessels which branched and developed high epithelium in such a manner as to cause histologic resemblance to glandular tissue.

Embryologists have derived the carotid bodies from the third branchial cleft (from the thymus), from the thyroid anlage and from the sheath of the carotid vessels. Kohn first recognized that the carotid bodies were composed of chromaffin tissue, and consequently their relationship to the sympathetic system.

In man the carotid bodies are two minute structures, 5 to 7 microns in length by 2.5 to 4 microns in breadth, each of which lies on the medial side of the corresponding common carotid artery at its bifurcation.

The only clinical importance of the carotid bodies is that they occasionally give rise to tumors, more than thirty-nine cases of which have been reported, the youngest in a 16-year-old girl. These tumors have never been accompanied by constitutional disturbance.

The function of the bodies has been investigated by Vassale, Frugoni, Schmidt and Betke. Frugoni injected extracts into animals and obtained results which are now recognized as the effects of tissue extract, such as fall in blood pressure, collapse, etc. His conclusion was that the carotid bodies were organs of internal secretion, having a depressing influence on blood pressure.

Schmidt excised the carotid bodies in two stages by first removing the bifurcating portion of the carotid artery on one side with its carotid body and subsequently the carotid artery and body of the other side. Since he obtained no symptoms or pathologic changes as a result of his extirpation experiments, he concluded that the bodies are functionless rudiments.

Betke²¹ repeated Schmidt's experiments on dogs and cats. He noted no changes for from four to eight weeks, but after that latent period had elapsed, there occurred retardation in growth, increasing weakness and cachexia, which led after a few months to death. The necropsies showed no cause of death in either abdomen or thorax. The chief pathologic changes were found in the skeleton and the spleen. The skeleton showed both microscopic and macroscopic evidences of rickets; the spleen showed a disappearance of the follicles, in some instances accompanied by an increase in the connective tissue; large cells of the megalokaryocyte type were numerous. The bone marrow was characterized by atrophy of the marrow cells.

Betke concluded that the carotid bodies are essential to life and

21. Betke: Experimentelle Untersuchungen über die physiologische Bedeutung der Glandula carotica, Beitr. z. klin. Chir., 1915, xcv, 343.

are, therefore, to be considered among the most important organs of internal secretion, belonging to the group which presides particularly over the growth of bone, and that they probably have some influence on blood formation.

It is interesting to note that Betke's experiments were published from Rehn's clinic in Frankfort, where the experiments of Klose and of Flesch on the thymus were also performed. All three investigators, the one extirpating the carotid bodies, the other two the thymus, obtained almost identical results. The coincidence in the results of such widely different experiments suggests that some common factor, unrelated to the removal of either thymus or carotid bodies, may have been operative, such as infection, confinement, poor care, or improper food, or a combination of these, giving rise to illness characterized by the gradual development of rickets and ending finally in death, making its appearance among those animals subjected to operation.

In any event, it is difficult to imagine that the carotid bodies can be essential to life, if it is true that they are merely aggregations of chromaffin tissue, when it is considered that chromaffin tissue is widely distributed in the body and even the comparatively immense mass of chromaffin tissue comprising the medullary portions of the adrenal glands is not essential to life.²² Further proof must be offered before Betke's work can be accepted.

THE PARATHYROIDS

Not much important literature on the subject of the parathyroid glands has appeared during the past two years.

Thimm²³ points out that the presence of more than two parathyroids on a side does not mean that the anlagen were more than their usual number.

In almost all the higher mammals parathyroid III is the lowermost, that is, the more caudally situated of the two parathyroids, but since it takes origin from the third pharyngeal pouch, while parathyroid IV, as its name indicates, develops from the fourth pharyngeal pouch, its original position in the embryo was above (cephalad to) that of parathyroid IV. The explanation of the more caudal position of parathyroid III lies in the fact that during its development it descends from its place of origin at the third pharyngeal pouch in company with the thymus cord, also derived from the third pharyngeal pouch, in the course of the migration of the latter downward (caudalward) toward the thorax, and comes to rest in most species of animals near the lower

22. Biedl: *Innere Sekretion*, 1916.

23. Thimm, L.: *Zur Kenntnis der Epithelkörperchen (Glandulae parathyreoideae)*, *Arch. f. Kinderh.*, 1914, lxiii, 321.

pole of the thyroid, but in the rabbit descends farther, so as to lie often considerably below the thyroid, usually in the substance of the thymus gland. Parathyroid III is the larger and more constant of the two parathyroids.

To return now to Thimm's paper: When there are more than two parathyroids on a side, the meaning is that parathyroid III was drawn out during its fetal descent into a thin cord, which became either actually broken up into a number of fragments, each forming a separate parathyroid, or else so thinned in places as to give the appearance of several separate parathyroids, when in reality thin strands of parathyroid tissue (often so minute as to be capable of demonstration only on microscopic examination of serial sections) joined them together in a continuous chain.

- There is rarely, if ever, more than one parathyroid derived from the fourth pharyngeal pouch on a side, and not always even one. For example, in the guinea-pig parathyroid²⁴ IV is frequently absent or rudimentary.

Fulci and Giannuzzi²⁵ extirpated some of the parathyroids in rabbits and studied the parathyroid tissue that remained for resulting histologic changes. Though the rabbits died five or six days after the operation, with the symptoms of parathyroid tetany, the investigators were able to detect in the parathyroid rests signs which they interpreted as regeneration. Epithelial strands passed from the main mass or masses of parathyroid tissue into the surrounding connective tissue, like the extensions from a neoplasm; some of the cells of the strands were undergoing division and young blood vessels were visible. They observed the same signs of regeneration in the parathyroid tissue of older animals after incomplete parathyroidectomy, as well as in the parathyroids of younger animals.

Thimm's work suggests that Fulci and Giannuzzi might have mistaken the strands connecting separate masses of parathyroid tissue for regenerating parathyroid. In any event, their work is not very convincing.

Jackson²⁶ investigated the effects of inanition on the parathyroids of rats. The parathyroids did not appear to be reduced in young rats by inanition, but in older rats to an extent commensurate with the loss

24. Ruben, R.: Zur Entwicklung der Thymus und der Parathyreoidea beim Meerschweinchen, *Anat. Anz.*, Jena, 1911, xxxix, 571.

25. Fulci, F., and Giannuzzi, A.: Ueber die Regenerationsfähigkeit der Parathyreoidea (Vorläufige Mitteilung), *Centralbl. f. allg. Path. u. path. Anat.*, 1915, xxvi, 97.

26. Jackson, C. M.: Effects of Inanition on the Structure of the Thyroid and Parathyroid Glands of the Albino Rat, *Anat. Rec.*, 1916, x, 208.

of body weight. He found that the parathyroid is less apt to develop structural changes during starvation than the thyroid and that normal variations in the histology of the parathyroids are less marked than in the thyroids.

By far the most important experimental work on the parathyroids which has appeared during the past two years is that of MacCallum, Lambert and Vogel.²⁷ These investigators performed experiments on dogs to show in a new way that the increased excitability of the peripheral nerves in tetany is caused by the lowered calcium content of the blood. The calcium content of defibrinated dog's blood was reduced in their experiments by means of the dialysis method of Abel, Rown-tree and Turner; that is, the blood was passed repeatedly through a series of celloidin tubes immersed in a fluid which had the same inorganic composition as dog's blood, with the exception that calcium was absent. By dialyzing dog's blood against this fluid the calcium content of the blood was reduced, for example, from 0.0364 gm. to 0.0284 gm. per liter. But the dog's blood could not be rendered calcium free by this method.

When the defibrinated blood with its reduced calcium content was perfused through the isolated extremity of a dog, increased excitability of the nerves was obtained, as determined by the galvanic current. But when the calcium-reduced blood was introduced into a living animal, that is, substituted for the normal blood of the animal, no such lowering of the excitability of the peripheral nerves took place, for the apparent reason that the calcium of the tissues of the dog passed over so readily into the calcium-reduced blood as speedily to make up the previously created deficiency in the latter. It is a well-known fact that the introduction of normal blood into an animal suffering from tetany stops the symptoms of tetany for a time. But when calcium-reduced blood was introduced into an animal suffering from parathyroid tetany no improvement of the symptoms resulted, thus demonstrating again the dependence of the symptoms of tetany on the lowered calcium content of the blood.

The authors advance the hypothesis that the function of the parathyroid may be to convert the "nondialyzable calcium into a dialyzable form, which latter is essential for the control of the excitability of the nerves, but which is lost in the excreta and not newly formed in the absence of parathyroid secretion."

27. MacCallum, W. G., Lambert, R. A., and Vogel, K. M.: The Removal of Calcium from the Blood by Dialysis in the Study of Tetany, *Jour. Exper. Med.*, 1914, xx, 149.

THE PINEAL GLAND²⁸

The pineal gland was selected by Descartes (1628) as the probable seat of the soul, on account of its central position in the brain and its proximity to the ventricles. It has been considered as a possible organ of internal secretion only since other structures of doubtful significance to the body have been found to be glands of internal secretion of vital importance. Embryologically, the pineal gland is the vestigial remnant of the pineal eye of the reptiles and certain other lower forms.

Gutzeit²⁹ in 1896 reported a case of teratoma of the pineal in a 7-year-old boy with precocious sexual development. Oestreich and Slawyk³⁰ in 1899 reported another case and almost simultaneously Ogle³¹ reported a third case of pineal teratoma, both of them in boys less than 7 years old showing precocious sexual development. By 1907 enough case reports of tumor of the pineal had accumulated in the literature for Marburg³² to collect forty-one, including his own. Although only two of Marburg's forty-one cases of pineal tumor showed precocious sexual development, and only a very small number a bodily development exceeding the normal, and in spite of the fact that no experimental work has been done on the pineal which could be used as a basis for speculation (Dandy), Marburg enunciated three clinical syndromes. Hyperpinealism, according to Marburg, gave rise to adiposity; apinealism, to cachexia; and hypopinealism to precocity of sexual development and to hypertropic conditions of the genitalia.

Since Marburg's publication other cases of pineal tumor have been added to the list, bringing the total number, according to Horrax, to seventy. But in only two of these more recently reported cases have there been the symptoms of precocious sexual development, one, the case of von Frank-Hochwart³³ (1909) in a boy 5½ years old, the other, Horrax's own case (1916). Horrax has reported, in addition to the case of pineal tumor just mentioned which was made certain by necropsy, two additional cases thought to be pineal tumor on purely clinical grounds, but on such slim evidence as to make consideration of them unnecessary.

28. A review of the entire subject by Kidd up to 1913 will be found in the *Review of Neurology and Psychiatry*, xi, 1-24 and 55-75. Marburg, *Ergebn. d. inn. Med. u. Kinderh.*, 1913, x, 146, gives a complete discussion of the subject in its clinical aspects. Horrax: *Arch. Int. Med.*, brings the bibliography up to date and gives an excellent résumé of the literature.

29. Gutzeit: *Ein Teratom der Zirbeldrüse*, Diss. Königsberg; cited by Kidd.

30. Oestreich and Slawyk: *Virchows Arch. f. path. Anat.*, clvii, 475; cited by Kidd.

31. Ogle, *Trans. Path. Soc., Lond.*, Vol. 50, p. 6.

32. Marburg: *Wein. med. Wchnschr.*, 1908, xlviii; *Arbeiten a. d. Wiener neurol. Inst.*, 1906, xiii, 288; *Ibid.*, 1909, xvii, 217; *Ergebn. d. inn. Med. u. Kinderh.*, 1913, x, 146.

33. Frankl-Hochwart: *Deutsch. Ztschr. f. Nervenh.*, 1909, xx, 455; cited by Horrax.

Horrax³⁴ authenticated case of pineal tumor was that of a boy aged 12 years, who had always been well except for asthmatic attacks until three and one-half months before his admission to the Brigham Hospital. There they noted that the patient was a lean boy, weighing 97 pounds, with some pigmentation of the skin, unequal pupils, choked disk, diplopia on looking to the right, suggestive Romberg, positive Kernig's sign, some stiffness of the neck and ataxia of the left arm. The symptoms, which had been observed during the three and one-half months prior to his admission to the hospital, were dilated and unequal pupils, a staring expression, blurred vision, headache, nausea and vomiting. The case was thought probably to be tuberculous meningitis. When, however, the necropsy revealed pineal tumor, certain other symptoms which apparently had not been sufficiently prominent to attract due attention were recalled. The boy, though lean, had gained 40 pounds³⁵ during the year preceding his acute illness; the pigmentation of the skin was distributed differently from that of sunburn; the genitalia were developed in advance of the age; there was a little pubic hair and the down on his face was in excess of the normal.

The important fact which the clinical study of tumors of the pineal gland brings out is that out of a total of seventy cases reported in the literature, symptoms of precocious sexual development appear in only five, and excessive growth in not more than seven. The study of case reports of pineal tumor, therefore, raises the inquiry whether the pineal gland has in reality anything to do with either sexual or physical development; in other words, whether precocious sexual development or growth occurring in cases of pineal tumor can not be explained by pressure effects on neighboring structures (the hypophysis?).

The most important symptoms of pineal tumor from the standpoint of diagnosis are the focal symptoms produced by the pressure of the tumor against the corpora quadrigemina and underlying structures, with resulting rather characteristic involvements in the distributions of the oculomotor nerves on both sides, and vertigo. The focal symptoms are usually accompanied by general symptoms of tumor. It may be said that if precocious sexual or physical development is present in a given case, unaccompanied by any focal symptoms pointing definitely to the pineal, it is probable that the cause lies elsewhere than in the pineal gland.

Cysts are the most frequent form of pineal tumor and next to cysts, teratomas. All five cases of pineal tumor showing precocious sexual development have been teratomas of the pineal. Hemorrhage into the

34. Horrax, Gilbert: Studies on the Pineal Gland. I. Experimental Observations, *Arch. Int. Med.*, 1916, xvii, 607.

35. He weighed 114 pounds at the beginning of his illness.

pineal and abscess of the pineal have been reported, and also tuberculous and syphilitic involvements.

The experimental attempts to determine the existence of pineal function have followed the usual lines employed in the determination of the function of organs of internal secretion, namely, feeding and injection experiments and extirpation of the gland.

Extirpation of the pineal gland has been performed by Sarteschi³⁶ in 1910 (rabbits) and in 1913 (puppies and guinea-pigs); by Biedl³⁷ in 1910 (dogs); by Exner and Boese³⁸ in 1910 (rabbits); and by Foà³⁹ in 1912 and 1914 (chickens). Sarteschi had very few survivals from his experiments. One puppy gained more rapidly in weight than the control puppy and at autopsy it was found that the testes were larger than those of the control. Biedl's three surviving dogs⁴⁰ showed no effects. Exner and Boese's six surviving rabbits remained normal. Foà succeeded in his first set of experiments in bringing three pinealectomized cocks and twelve hens to maturity. The pinealectomized cocks crowed and were sexually active from forty-two to seventy-nine days before their controls, and developed hypertrophied combs and testes. In his second set of experiments two male and five female chickens survived. The two males developed in exactly the same way as the males of the first set of experiments. But the females in both sets of experiments remained entirely normal. Foà also removed the pineal gland from a few rats, with indefinite results very similar to those obtained by Horrax.

Adler, attracted by the experiments of Foà, investigated pineal function in the frog. The frog larva seemed to be particularly adapted for demonstration of the effects of extirpation of the pineal. For if the pineal regulates in some special way growth and development, its activity should be intense at the period of metamorphosis from the larval state, and consequently the changes produced by its removal should become very evident as the period of metamorphosis falls due. In the second place the phenomenon of sudden transition from tadpole to frog, at about the tenth to the thirteenth week, afforded a splendid means of measurement of any influence on the development and growth of the animal.

Adler⁴¹ pinealectomized by means of the thermocautery 850 tad-

36. Sarteschi, U.: *Folia Neurobiologia*, Vol. iv, No. 6; cited by Kidd.

37. Biedl, A.: *Innere Sekretion*, 1913, p. 194.

38. Exner and Boese: *Deutsch. Ztschr. f. Chir.*, 1910, cvii, 182; *München. med. Wehnschr.*, 1911, i, 154; *Neurol. Centralbl.*, 1910, 754.

39. Foà, C.: *Arch. ital. de biol.*, 1912, lvii, 233; *Ibid.*, 1914, lxi, 79; *Pathologica*, iv, 445.

40. Biedl's dogs were fully grown at the time of operation.

41. Adler: 'Extirpation der Epiphyse, *Arch. f. Entwicklungsch. d. Organ.*, 1914, xl, 1.

poles, averaging 21 mm. in length. However, a very small number of them survived the operations and the subsequent period of observation. His operative frogs showed no differences in growth or development, which he felt justified in referring to the removal of the pineal. When he killed the surviving animals two months after the pinealectomy, he was unable to find any changes in thyroid, hypophysis, thymus, or in the testis. He concluded, therefore, that the pineal does not exercise in the frog the functions which were indicated by Foà's experiments in the fowl.

Dandy⁴² (1915) was the first to devise a satisfactory experimental method for removal of the pineal gland in dogs. The methods used by the investigators already mentioned were accompanied by a high mortality, due to hemorrhage from the veins of Galen, which are in close proximity to the pineal gland. Dandy's method depends on an exposure of the pineal by incision through the corpus callosum. He used dogs varying in age from 10 days to 3 weeks, the exact number of which are not stated in his publication. One of his animals was alive fifteen months after the operation; one died of distemper one year afterward; and several survived three to eight months, dying of some condition entirely unrelated to the pineal. Dandy's experiments were hampered by the distemper and mange. He was unable to detect any change in his animals in their sexual or physical development, or in the histology of any of the organs, including the organs of internal secretion. He concluded that the pineal is not essential to life and that removal of the gland in dogs furnishes no evidence that it possesses a function.

The most recent pineal extirpations are those of Horrax³⁴ in guinea-pigs and rats. Out of a large number of guinea-pigs Horrax succeeded in removing the pineal completely in fifteen males and twenty females, which were able to survive the operation. His animals were 2 days to 7 weeks old at the time of the operation, and were kept under observation for periods varying from seven and one-half to fourteen weeks. He controlled his operative animals chiefly but not entirely from the same litters and performed on the controls sham operations, stopping short of removal of the gland. Horrax found that loss of the pineal was not followed by any change in the weight curve. He did find, however, that the testes of the male animals of his operative series outweighed those of the controls, averaging 12.8 gm. as opposed to 9.9 gm., the average weight of the testes of the controls. Between the ninth and eleventh weeks minor histologic changes were found; but in younger animals none were present, and in older animals

42. Dandy, W. E.: Extirpation of the Pineal Body, *Jour. Exper. Med.*, 1915, xxii, 2.

the changes, if formerly present, had disappeared. The changes noted in the period between the ninth and eleventh weeks were larger tubules and more signs of spermatogenesis than in the testes of the control animals. The seminal vesicles of the operative guinea-pigs also appeared to be the more distended and to contain a colloid substance in greater abundance. The female animals in Horrax' experiments seem to have been essentially unaffected, although he thought he could discern a tendency toward earlier conception.

Horrax' pinealectomies in rats showed really nothing except that the operation was feasible in that species of animals, for his experimental material was killed off in large part by an epidemic.

Horrax draws two conclusions from his experiments, that the loss of the pineal hastens the growth and maturation of the testes and tends to accelerate sexual maturity in the females.

Howell,⁴³ 1908, Dixon and Halliburton,⁴³ 1909, Jordan and Eyster,⁴³ 1911, Ott and Scott,⁴³ 1912, injected pineal extract into animals, obtaining on the whole negative results. Horrax, using pineals from young calves and sheep to make his extract, obtained a fall in blood pressure. McCord⁴⁴ also obtained a drop in blood pressure by injection of pineal extract into animals, and in some instances even death. Both investigators attributed the fall to the physiologic action of the internal secretion of the pineal gland.

Dana and Berkeley⁴⁵ have performed feeding experiments on young guinea-pigs, kittens and rabbits. They found that the animals fed with pineal gained weight more rapidly than the control animals. They then fed pineal glands to defective children, including mongolian idiots, and found that their mental progress was more rapid, though they did not gain in weight so rapidly as the control children.

The most numerous feeding experiments have been done by McCord.⁴⁴ He fed powdered extract of pineals taken from animals of different ages to guinea-pigs, puppies, adult dogs and chicks with remarkable results. He found that chickens fed with the extract of the pineals of young animals gained in weight more rapidly than the control chickens, but that when they were fed extract from pineals of mature cattle, they gained no more rapidly than the controls. In his feeding experiments on guinea-pigs he found a symmetrical overgrowth of the pineal-fed guinea-pig and also an acceleration of sexual

43. For references to the work of these investigators consult Kidd or Horrax.

44. McCord, C. P.: The Pineal Gland, *Interstate Med. Jour.*, 1915, xxii, 354; The Pineal Gland in Relation to Somatic, Sexual and Mental Development, *Jour. Am. Med. Assn.*, 1915, lxxv, 517.

45. Dana, C. L., and Berkeley: The Functions of the Pineal Gland, *Med. Rec.*, New York, 1913, lxxxiii, 835; cited by Horrax. Berkeley, W. N.: The Use of Pineal Gland in the Treatment of Certain Classes of Defective Children, *Med. Rec.* New York, 1914, lxxxv, 513; cited by Horrax.

maturity, as demonstrated by the fact that with but two exceptions young guinea-pigs were born to the pineal-fed females left to breed naturally with pineal-fed males earlier than young were born to the control females bred to control males. McCord's experiments on puppies were rendered of little value because of an epidemic of distemper. Nevertheless, he thought he could detect more intelligence in the pineal-fed dogs than in the controls, as well as increased growth. He remarks that when his experiments were finished only the pineal-fed dogs were in demand as pets.

It seems probable that a mass of experimental literature of a conflicting nature will develop about the pineal body, like that which has sprung up around the thymus and the spleen. It can now be said that the experimental work on the pineal up to the present time has failed to prove that it possesses a function. The results of Foà, which were negative in the pullets and positive only in a few cocks, cannot be regarded as in any way final. The changes which Horrax obtained were so slight as to make it seem remarkable he should have regarded his experiments as positive. If the extraordinary results which McCord obtained by feeding pineal were actually caused by the active principle of the gland, the extirpation experience of Dandy and Horrax ought to have brought overwhelming evidence of pineal function and clinical literature to abound with examples of pineal disease.

THE PITUITARY

Keeton and Becht⁴⁶ found that direct electrical stimulation of the hypophysis caused an increase in the reducing substance of the blood, while stimulation of the brain in front of and behind the hypophysis failed to produce any increase in the reducing substance. The increase did not take place in dogs whose splanchnic nerves had been cut—a finding not in accord with the theory held by Cushing and others that it is the hormone discharged by the hypophysis into the blood which causes mobilization of the glycogen.

Dandy and Goetsch⁴⁷ have shown that fibers from the sympathetic are sent to the pituitary body. By stimulating the cervical sympathetic ganglia Shamoff⁴⁸ obtained glycosuria and diuresis in eight out of fifteen animals tested. All nervous pathways from the stimulated ganglion to the kidneys had been cut. Shamoff, therefore, arrived at the opposite conclusion from Keeton and Becht, namely, that it was the secretion of the hypophysis thrown out into the blood stream as a

46. Keeton, R. W., and Becht, F. C.: The Stimulation of the Hypophysis in Dogs. *Am. Jour. Physiol.*, 1915, xxxix, 109.

47. Dandy and Goetsch: *Am. Jour. Anat.*, 1910, xi, 137; cited by Shamoff.

48. Shamoff, V. N.: Concerning the Action of Various Pituitary Extracts on Isolated Intestinal Loop. *Am. Jour. Physiol.*, 1915-1916, xxxix, 268.

result of stimulation of the sympathetic which produced glycosuria and diuresis, especially in view of the fact that the response obtained was a typical pituitary response, as was indicated by the combination of increased blood pressure, glycosuria and polyuria.

Weed and Cushing⁴⁹ determined that extract of the posterior lobe of the hypophysis introduced intravenously into animals caused an increase in the rate of production of the cerebrospinal fluid. The increase obtained appeared to be independent of respiratory or hemodynamic influences. The authors consequently thought that it was due to the specific action of some substance in the posterior lobe of the hypophysis on the choroid plexus, stimulating it to increased secretory activity.

McCord⁵⁰ found that the pituitary in eight-year-old bovine fetuses showed the presence of the active principle as determined by the method of Dale and Laidlaw.⁵¹ McCord believes the active principle of the pituitary is present in fetal life as early as the gland is capable of macroscopic recognition.

Lewis⁵² found that the quantity of pressor substance contained in the hypophysis of the pig fetus of 175 mm. was sufficient to indicate that a pig fetus of this size is independent of its mother's hypophysial secretion. Lewis discovered evidences of the pressor substance in the hypophysis of pig fetuses 125 mm. long.

Fenger⁵³ attempted to determine by the use of the uterus strip method of Fraenkel whether a seasonal variation in the secretory activity of the posterior lobe of the hypophysis could be demonstrated, but was unable to find any difference in the extracts from summer and winter glands.

The literature of the past two years contains reports of a number of experiments in pituitary feeding which have given quite discordant results.

Pearl and Surface⁵⁴ obtained no evidence that the hypophysis activates the resting ovary of the hen.

49. Weed, L. H., and Cushing, H.: Studies on the Cerebrospinal Fluid. VIII. The Effect of Pituitary Extract on the Secretion (Choroidorrhea), *Am. Jour. Physiol.*, 1914-1915, xxxvi, 77.

50. McCord, C. P.: The Occurrence of Pituitrin and Epinephrin in Fetal Pituitary and Suprarenal Glands, *Jour. Biol. Chem.*, 1915, xxiii, 435.

51. Dale, H. H., and Laidlaw, P. P.: *Jour. Pharm. and Exper. Therap.*, 1912-1913, iv, 75; cited by McCord.

52. Lewis, D.: The Appearance of Pressor Substance in the Fetal Hypophysis, *Jour. Exper. Med.*, 1916, xxiii, 677.

53. Fenger, F.: On the Composition and Physiological Activity of the Pituitary Body, *Jour. Biol. Chem.*, 1915, xxi, 283.

54. Pearl, R., and Surface, F. M.: Studies on the Physiology of Reproduction in the Domestic Fowl. XIII. On the Failure of Extract of Pituitary Body (Anterior Lobe) to Activate the Resting Ovary, *Jour. Biol. Chem.*, 1915, xxi, 95.

L. M. Clark⁵⁵ found, on the other hand, that feeding of the pituitary gland (the anterior lobe) of young cattle to hens raised the egg production curve at a time when the latter was normally on the decline. The effect was noticed four days after feeding was begun and lasted for a number of days after it had been stopped. He observed, further, that a greater percentage of eggs hatched when both parents had received pituitary feeding than when no pituitary was used.

Pearl,⁵⁶ who also fed desiccated substance of anterior lobe of hypophysis to hens at the period of decline in egg production, could find no evidence that it produced any effect. He came to the conclusion that feeding of the pituitary to growing pullets does not bring about earlier activation of the ovary. The feeding of the anterior lobe to chicks, however, produced a retardation in growth.

Robertson⁵⁷ studied the effects of pituitary feeding on the growth of mice. The administration of 0.125 gm. per day of anterior lobe pituitary tissue to mice, begun in the fourth week, led to retardation of growth during the earlier portion of what Robertson terms "the third growth cycle," that is, between the sixth and twentieth weeks; but from the twentieth to the sixtieth week, in the latter part of "the third growth cycle," to an acceleration of growth, so that the pituitary-fed mice caught up to and surpassed the controls. Robertson further observed that pituitary-fed animals from the thirtieth week onward appeared more compactly built than the controls. Though "weight for weight they were smaller, size for size they were heavier." He also observed that the pituitary-fed animals showed marked belligerency.

Robertson⁵⁸ thinks he has isolated the active principle of the anterior lobe of the pituitary, which affects growth, giving it the name "tethelin." The effects on mice obtained by its administration were identical with those which followed the administration of the entire gland. It is prepared by extracting the dried tissue of the anterior lobe of the pituitary with boiling alcohol and precipitating with ether.

Robertson⁵⁹ investigated the effects of extracts of the anterior lobe

55. Clark, L. N.: The Effect of Pituitary Substance on the Egg Production of the Domestic Fowl, *Jour. Biol. Chem.*, 1915, xxii, 485.

56. Pearl, R.: Studies on the Physiology of Reproduction in the Domestic Fowl, *Jour. Physiol. Chem.*, 1916, xxiv, 123.

57. Robertson, T. B.: Experimental Studies on Growth. III. The Influence of the Anterior Lobe of the Pituitary Body on the Growth of the White Mouse, *Jour. Biol. Chem.*, 1916, xxiv, 385.

58. Robertson, T. B.: On the Isolation and Properties of the Anterior Lobe of the Pituitary Body, *Jour. Biol. Chem.*, 1916, xxiv, 409.

59. Robertson, T. B., and Burnett, T. C.: The Influence of the Anterior Lobe of the Pituitary Body on the Growth of Carcinomata (Preliminary Communication). *Proc. Soc. Exper. Biol. and Med.*, 1914, xii, 68; *Jour. Exper. Med.*, 1915, xxi, 280.

of the hypophysis on the growth of carcinomas inoculated into rats. He found that emulsion of the anterior lobe of the ox pituitary markedly increased the rate of growth of the primary tumor and that small tumors were affected even more than large tumors. But the acceleration in growth was evidenced only at a certain stage in the growth of the tumor, subsequent to the twentieth day after inoculation.

Goetsch⁶⁰ also has made feeding experiments with the pituitary gland to determine the effects on growth and sexual development. He used white rats, choosing stock of known pedigree, in order to reduce normal variation in his material to the lowest possible point. He conducted separate experiments, using the dried, powdered extract of the entire hypophyses and of the anterior and posterior lobes, respectively.

When dried extract of the entire gland was fed to young rats in excessive doses (0.1 gm. daily), it caused failure to gain in weight, loss of appetite, diarrhea, muscular weakness and tremor. These symptoms Goetsch attributed to the activity of the posterior lobe element. When whole gland was fed in smaller dosage, it caused within from twenty-five to forty days a more rapid growth and development, larger nipples in the females, and a more coarse, harsher coat of hair than in controls fed on the same diet. Some of the controls received ovarian extract in the same dosage as that of the hypophysis. The influence of whole gland feeding on the sex glands of the female was to make the ovaries, tubes and cornua of the uterus larger and more vascular than those of the controls and maturity of the ovary to occur one or two months before the normal time. Maturity of the ovary was indicated by active ovulation and Graafian follicle formation. The effect of whole gland feeding on the genital organs of the male was the production of a more rapid growth and development of the testes, an earlier descent, precocious spermatogenesis occurring at a time when the testes of the controls were still immature.

The feeding of anterior lobe alone caused increased weight, greater and more vigorous body growth and an earlier and more active genital development, but without the diarrhea and nervous manifestations seen at the beginning of whole gland feeding. The period of sexual development was shortened by at least one month. That feedings of the anterior lobe produced earlier and greater sexual activity was demonstrated by the fact that a male and a female fed with anterior lobe over a period of from eight to nine months bred earlier and oftener than a control pair, producing two litters in seven months, while the control pair had no offspring. The effect of continued

60. Goetsch, E.: The Influence of Pituitary Feeding on Growth and Sexual Development. An Experimental Study, *Bull. Johns Hopkins Hosp.*, 1916, xxvii, 29.

anterior lobe feeding on the sex glands held throughout the life of the animal and was greater, the longer had been the period of administration. Its stimulating effect on the parents was seen in the offspring in intrauterine development and during lactation; and when feeding of the offspring with anterior lobe was begun as soon as lactation from the hypophyseal-fed mother had come to an end, the very maximal effects were produced.

Posterior lobe feeding did not stimulate growth or the development of the sex glands; in fact, it seemed to retard the development. In large doses it caused a diarrhea, with loss of weight.

It might be mentioned that ovarian extract, Goetsch found, had a stimulating influence on the sexual development of the female, but a retarding influence on that of the male.

Solem and Lommen⁶¹ have found that injection of pituitary extract causes a decrease in the flow of saliva. In their opinion the decrease is brought about by the constricting action of pituitary extract on the arterioles of the salivary glands, which diminishes their blood supply and also by its specific inhibiting influence on the secretory nerves of the glands.

Simpson and Hill⁶² have studied the effect of pituitary extract on milk production. Their conclusion is as follows:

The administration of pituitary extract, by intravenous, intramuscular or subcutaneous injection, to a lactating animal leads to a marked increase in the quantity of milk secreted and also in its fat content. In the goat, if the injection be continued at intervals over a prolonged period—several months—immunity to its action on the mammary glands appears to be established both in regard to the amount of milk yielded and the percentage of fat it contains.

Livingston⁶³ castrated and spayed rabbits to determine any resulting alterations in the weight of the organs of internal secretion, in particular the hypophysis. He found that though hypertrophy of the hypophysis did not regularly follow spaying or castration, it usually occurred and was a commoner development in females than in males. On the other hand, he discovered that a constant relationship did exist between increase in body weight and hypertrophy of the hypophysis, that is, an increase in the size of the hypophysis was accompanied by increased rate of growth and vice versa. No effect on the suprarenals or thyroid could be detected.

61. Solem, G. O., and Lommen, P. A.: The Influence of the Extract of the Posterior Lobe of the Hypophysis on the Secretion of Saliva, *Am. Jour. Physiol.*, 1915, xxxviii, 339.

62. Simpson, S., and Hill, R. L.: The Effect of Repeated Injections of Pituitary Extract on Milk Secretions, *Am. Jour. Physiol.*, 1914-1915, xxxvi, 347.

63. Livingston, A. E.: The Effect of Castration on the Weight of the Pituitary Body and Other Glands of Internal Secretion in the Rabbit, *Am. Jour. Physiol.*, 1916, xl, 153.

Cushing and Goetsch⁶⁴ have made an interesting study of the organs of internal secretion in seven hibernating woodchucks. They found changes of a minor character in several of the organs of internal secretion, but the most definite changes in the hypophysis. The latter was reduced in size, and the cells of the pars anterior in some of the animals had lost their characteristic staining reactions to acid and basic dyes. After hibernation was over, the gland regained its normal size and the cells their normal staining properties and showed signs of division. Their conclusion is as follows:

On the basis of these observations hibernation may be ascribed to a seasonal physiological wave of pluriglandular activity. The essential rôle may perhaps be ascribed to the pituitary body, not only for the reason that the most striking histological changes appear in this structure, but also because deprivation of the secretion of this gland alone of the entire ductless gland series produces a group of symptoms comparable to those of hibernation.

They base the conclusion just given on an analogy. Human beings with hypopituitarism have shown storage of fat, slow pulse and respiration, extreme somnolence and subnormal temperature. The hibernating animal shows exactly this same group of symptoms. The histologic changes in the hypophyses of both are similar. Since the alteration in the hypophysis appears to be the cause in the one, it must be the chief cause at least of the other. Cushing and Goetsch point out that the theory originated with two Italians, Salmon (1905) and Gemelli (1906), both of whom, however, had, in Cushing and Goetsch's opinion, an incorrect conception of the mode of activity of the hypophysis.

Their conclusion that hibernation is the result of a "wave of pluriglandular inactivity" with the hypophysis playing "the essential rôle" forms an attractive hypothesis.

Fry⁶⁵ has made histologic studies of the pituitary in eight cases of diabetes, two of myxedema, one of cystic goiter, one of Addison's disease and one of status lymphaticus. In the hypophysis of diabetes he found an increase in the chromophil cells, which appeared as adenomatous masses, evidences of conversion of chromophil cells into colloid and, in some instances, degenerative changes which were so extensive that few of the cellular elements in the anterior lobe remained. He believed these changes were not a part of a general reaction of the body tissues to the disease, but indicated that the hypophysis was primarily affected and consequently that it might be primarily concerned in the causation of diabetes. In the case of myxedema he

64. Cushing, H., and Goetsch, E.: *Hibernation and the Pituitary Body*, *Jour. Exper. Med.*, 1915, xxii, 25.

65. Fry, H. J. B.: *The Pituitary Gland in Diabetes Mellitus and Disorders of the Glands of Internal Secretion*, *Quart. Jour. Med.*, 1915, viii, 278.

found the pituitary increased in weight; in the case of goiter showing a hyperplasia of chromophil cells, an increase of colloid in the interglandular cleft, but unchanged in Addison's disease and status lymphaticus. He advanced a theory of explanation of the secretory mechanism of the hypophysis which need not be discussed here.

Riese⁶⁶ reports favorable results⁶⁷ from the use of hypophysis extract in asthma, comparable to those obtained by the use of epinephrin. Similar results had been obtained previously by Borchardt (Riese).

Numerous case reports appear in the literature indicating a favorable effect following the use of hypophysial extract in diabetes insipidus. Grøndahl¹⁷ reports a case of diabetes insipidus accompanying hypophysial tumor in a 16-year-old subject who showed alimentary glycosuria, as well as polyuria and infantilism, and subsequently developed evidences of acromegaly. The polyuria was reduced from the neighborhood of 6 liters a day to about 2 liters by injections of pituitary extract.

Hoppe-Seyler⁶⁸ reports a case in which the urinary output ranged from 4 to 7 liters daily and the specific gravity of the urine was 1.002, treated by pituitary extract. Subcutaneous injections of pituitary extract repeatedly caused temporary reduction of the total urine to between 1 and 2 liters in twenty-four hours.

Graul⁶⁹ reports a similar case in which extract from the pars intermedia and posterior lobe was given hyperdermically with success.

Motzfeldt⁷⁰ reports three patients with diabetes insipidus, one of whom showed improvement when treated with pituitary extract. This case, which Motzfeldt reports in extenso, is particularly interesting in that the patient appeared to be benefited by taking hypophysial gland by mouth. It was necessary for him to take from five to seven glands

66. Riese, E.: Zur Wirkung des Hypophysenextraktes bei Asthma bronchiale und zur Asthmatheorie, Berl. klin. Wchnschr., 1915, lii, 768.

67. It is very easy to understand that epinephrin produces a favorable effect in asthma, but it is difficult to understand why pituitary extract should produce a favorable effect. Theoretically it should produce an unfavorable effect, because it constricts smooth muscle quite independently of the innervation. Riese's results cannot be accepted until corroborated.

68. Hoppe-Seyler, G.: Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandlung mit Hypophysenextrakt, München med. Wchnschr., 1915, lxii, 1633.

69. Graul, G.: Ueber einen mit Hypophysin-Höchst erfolgreich behandelten Fall von Diabetes insipidus, Deutsch. med. Wchnschr., 1915, xli, 1095.

70. Motzfeldt, K.: The Pituitary Gland and Diuresis. I. Diabetes Insipidus and Its Relation to the Hypophysis Cerebri. II. Studies on the Action of Pituitary Extract, Especially on Diuresis, Blood Pressure and Nitrogenous Metabolism in Relatively Healthy Men, Norsk Mag. f. Laegevidensk., 1915, xiii, 1305.

at a time, raw or dried and powdered, in order to obtain an effect comparable to "one quarter of a syringe full of commercial extract."

Von Konschegg and Schuster⁷¹ have obtained well-marked diminution in urinary output by the use of pituitary extract injections in both animals and man. The best results they obtained in human beings suffering from primary idiopathic diabetes insipidus. Their animal material was rabbits.

Pollock⁷² reported four cases of hydrocephalus accompanied by adiposity and tapering hands as probable examples of hypopituitarism, caused by the increased intracranial pressure on the hypophysis.

THYMUS

Badertscher⁷³ finds that the thymus of the pig is of both ectodermal and entodermal origin. The ectodermal derivative, he thinks, is constant and forms the "superficial thymus." Kastschenko⁷⁴ (1887) and Zötterman⁷⁵ (1911) also derive the thymus of the pig from both ectoderm and entoderm.

In the guinea-pig and mole⁷⁶ the thymus has also been traced to both ectoderm and entoderm, but appears to be purely entodermal in the other higher mammals investigated.

Marine⁷⁷ points out the frequency of duct-like spaces or tubules in the thymus of dogs. He was able to find them in 21 per cent. of the animals examined, but in only one human thymus out of a total of 126. Marine believes that these duct-like tubules are closely related in their origin to the Hassall corpuscles, both springing from the "embryonic thymic epithelial tubules and cords." He considers that in the case of the Hassall corpuscles the involutionary change took place before the differentiation into tubules occurred; in the case of the tubules differentiation occurred before the involutionary process began.

71. Von Konschegg, A., and Schuster, E.: Ueber die Blinflussung der Diurese durch Hypophysenextrakte, *Deutsch. med. Wchnschr.*, 1915, xli, 1091.

72. Pollock, L. J.: Hypopituitarism in Chronic Hydrocephalus, *Jour. Am. Med. Assn.*, 1915, lxiv, 395. There have appeared in the literature a number of cases of this nature. Indeed the diagnosis of hypopituitarism is frequently made in fat children who are otherwise normal, merely because they are fat. In this connection it is necessary to remember that many mentally defective children, and among them hydrocephalics, lead of necessity vegetative existences and receive diets high in carbohydrates. Consequently, they are especially prone to become fat.

73. Badertscher, J. A.: The Development of the Thymus in the Pig. I. Morphogenesis, *Am. Jour. Anat.*, 1914-1915, xvii, 317.

74. Kastschenko: *Arch. f. mikroskop. Anat.*, 1887, xxx; cited by Badertscher.

75. Zötterman, Agne: *Anat. Anz.*, 1911, xxxviii, 514.

76. Ruben, R.: *Anat. Anz.*, 1911, xxxix, 571.

77. Marine, D.: The Frequency of Duct-Like Spaces in the Thymus Gland with Remarks on the Formation and Fate of Hassall's Corpuscles, *Cleveland Med. Jour.*, 1915, xiv, 186.

Hart⁷⁸ also has made a study of the Hassall corpuscles. He states that they are without doubt derivatives of the epithelial elements of the thymus. On this point there is a very general agreement among all authors, although it has been maintained by some investigators that the Hassall corpuscles take origin from the endothelium of blood vessels (Afanassiew,⁷⁹ Barbarossa⁸⁰). According to Hammer,⁸¹ Hart and others the Hassall corpuscles are formed by a coalescence of the thymus reticulum (the epithelial element) very much as giant cells are formed about foreign bodies. Hart states, further, that Hassall's corpuscles are continually being formed so long as the thymus reticulum continues to exist. In this sense, then, the Hassall corpuscles are an index to the functional activity of the thymus. Hart is careful to state that he does not regard the Hassall corpuscles as the secretory element or representing the secretory mechanism of the thymus, as some writers on this subject have done (Magni⁸² Mensi,⁸³ Livini⁸⁴). He regards the epithelium of the thymus (the so-called reticular cells) as the true secretory element and the Hassall corpuscles merely as the index to the amount of epithelium present. "In a word, it is possible to estimate the functioning energy of the thymus by the kind and number of the Hassall corpuscles . . . and so draw conclusions in regard to the condition of the organ at the time of death." The formation of Hassall corpuscles is most active in childhood, and in pathologic conditions in which the thymus function is increased.

Cases of congenital status thymolymphaticus have been reported by Hedinger⁸⁵ (12 cases), Kayser,⁸⁶ Flügge,⁸⁷ Somma⁸⁸ and Durante,⁸⁹ but according to Schridde⁹⁰ it is not certain that they are all true cases, for, in the majority, data essential to the diagnosis are lacking, such as weight of the thymus or evidences of status lymphaticus outside the thymus itself. Schridde's⁹⁰ paper consists of a report of three cases of congenital status thymolymphaticus. In one case the thymus weighed 19 gm., in the second 24 gm., in the third 26 gm. The histo-

78. Hart, C.: Thymusstudien. IV. Die Hassallschen Körperchen, Virchows Arch. f. path. Anat., 1914, ccxvii, 239.

79. Afanassiew, B.: Arch. f. mikroskop. Anat., 14, 1877.

80. Barbarossa: *Pediatria*, 1911, Series 2, xix, 457.

81. Hammar, T. A.: Fünfzig Jahre Thymus Forschung, *Ergebn. d. Anat. u. Entwicklungsgesch.*, 1910.

82. Magni: Arch. f. Kinderh., 1903, xxxviii, 14.

83. Mensi: *Pediatria*, 1903, xi, 65.

84. Livini: Cited by Mensi (Footnote 83).

85. Hedinger: *Jahrb. f. Kinderh., New Series*, lviii, 308.

86. Kayser, J.: *Diss.*, Giessen, 1895.

87. Flügge: *Vierteljahrsschr. f. gerichtl. Medizin*, 1899, Series 3, xvii.

88. Somma: *Arch. de patol. infant*, 1884.

89. Hedinger: 310.

90. Schridde, H.: *Der angeborene Status thymolymphaticus*, München. med. Wechnschr., 1914, lxi, 2161.

logic picture of the thymus in all three cases was identical with that described by Schridde as characteristic of the thymus of postnatal status lymphaticus. In all three cases hyperplasia of the medulla of the thymus was present, and the lymph follicles of the spleen were enlarged so that they were visible to the naked eye and in two of the cases the follicles of the intestines were also macroscopically visible. All three were excellently nourished infants. The mother of one of them died of eclampsia soon after the birth of the child and showed at necropsy the lesions of status thymolymphaticus, a coincidence which at once suggested the possibility that the pathologic condition was hereditary. Schridde also examined the thymus gland in about fifty stillbirths not the subject of status lymphaticus and found that the difference in weight of the thymus at birth is considerable, varying from 5 to 20 gm.

The average which Hammar gives for the weight of the thymus in the normally sized child at birth is 13.26 to 14.4 gm.

It is well established that the thymus either continues to persist or undergoes a reviviscence in certain diseases, as, for example, very commonly in exophthalmic goiter and with considerable frequency in Addison's disease and myasthenia gravis.

Hart⁹¹ reports two cases of myasthenia gravis and discusses at some length the relationship of the enlarged thymus to the disease. He thinks the enlarged thymus of myasthenia gravis is a persistent thymus which has undergone hyperplasia, as the persistent thymus, in his opinion, tends to do, and that the aggregations of round cells are lymphocytic infiltrations. He attaches a twofold significance to the enlargement of the thymus in myasthenia. In the first place, he believes it indicates that the affected individual has the lymphatic constitution; in other words, is constitutionally inferior and, therefore, predisposed from birth to the development of such disturbances as exophthalmic goiter and myasthenia gravis. In the second place, Hart believes the thymus in myasthenia gravis exerts a pathologic function and is frequently, if it is not always, the cause of the disease. He states that removal of the hyperplastic thymus cures myasthenia gravis, basing his statement apparently on a single case in which the thymus was removed by Sauerbruch,⁹² but at the same time admits that there are cases of myasthenia gravis without hyperplasia of the thymus, a fact which is well known. He endeavors to extricate himself from the dilemma caused through this admission by saying that after all an enlarged thymus is only one of numerous stigmata of constitutional

91. Hart, C.: Thymusstudien. V. Thymus befunde bei Myasthenia gravis pseudoparalytica, Virchows Arch. f. path. Anat., 1915, ccxx, 185.

92. Reference not given by Hart.

inferiority and that absence of enlarged thymus does not mean that the subject of myasthenia may not be constitutionally inferior, and in the second place that the thymus, though involuted, may exert a deleterious influence, citing that now well-worn case of von Haberer's, in which great improvement took place in a patient acutely sick with exophthalmic goiter, when a part of the retrosternal fat body was removed. Hart seems to be attempting to transfer his theories of thymus function in exophthalmic goiter to the thymus in myasthenia gravis. His reasoning is not clear and his interpretation of the facts seems to be tuned to his theory. The important point in his article is his statement that removal of a hyperplastic thymus cures myasthenia gravis. The truth or falsity of this statement should be investigated.

Funk and Douglas,⁹³ on the other hand, call attention to the complete disappearance of the thymus in pigeons suffering from beriberi. Their studies are limited to eight pigeons, apparently uncontrolled. Although the thymus is supposed to persist throughout life in the pigeon, Funk and Douglas were unable to find even microscopic rests of the thymus in their beriberi pigeons. In addition to disappearance of the thymus they found changes in other organs of internal secretion. The thyroid showed a marked degeneration in two instances and in a third signs of inflammation. The pituitaries also showed degenerative changes. (Their findings in the pituitaries can scarcely have any value because of their method of preparation for histologic study, which must have made accurate histologic interpretation impossible.) The ovaries were reduced in volume: the testes, atrophied. The pancreas was small and showed areas of degeneration. The spleen also was diminished in size and showed absence of the malpighian bodies. The ages of the birds were not given.

The work of Funk and Douglas was assailed by Williams and Crowell.⁹⁴ These authors found that in human beings having beriberi involution of the thymus does not always occur. In some cases the thymus was found actually enlarged and in others even status lymphaticus present. In a beriberi subject of 13 years the thymus weighed 28 gm.; in another 18 years old, 12 gm. Their experimental study was made on sixteen chickens having beriberi. The thymus had disappeared in seven of the chickens, was atrophied in five, and was slightly if at all altered in four. There was no evidence of a relationship between the severity of the disease and the degree of atrophy of the thymus. Thymus tissue was fed to the beriberi birds without any effect. Williams and Crowell concluded that there is no fundamental

93. Funk, C., and Douglas, M.: Studies on Beriberi. VIII. The Relationship of Beriberi to Glands of Internal Secretion, *Jour. Physiol.*, 1914, xlvii, 475.

94. Williams, R. R., and Crowell, B. C.: The Thymus Gland in Beriberi, *Philippine Jour. Sc.*, 1915, x, 121.

connection between atrophy of the thymus and beriberi, and if a protective influence against beriberi is exerted by the thymus, as Funk in a previous paper had maintained, it is due to the pyrimidon and purin derivatives which are present in large amounts in thymus tissue.

Fenger⁹⁵ has made chemical studies of the fetal thymus to determine whether certain substances are present in it which are found in the postfetal thymus. He discovered that the fetal thymus contains nucleic bodies and phosphates in the same proportions as the glands of young growing animals. For this reason he inferred that the gland is active at least three months before birth. He points out incidentally that fetal animals have more thymus tissue per unit of body weight than animals after birth.

In the two or three years which preceded the period covered by this review, appeared the extensive publications of Klose and Vogt,⁹⁶ Klose, and of Matti⁹⁷ on the physiology of the thymus gland. Their experimental work indicated that the thymus was essential to life, had a profound influence on the growth and development of the body and presided especially over the metabolism of bone. Their thymectomized animals not only showed marked disturbances of growth, but developed rickets and well-marked changes in the thyroid and suprarenals. Klose and Vogt, and subsequently Klose, writing independently, reported in addition extensive lesions in almost all the organs, especially in the nervous system, which they referred to loss of the thymus, and even saw in the behavior of their thymectomized dogs a condition of "thymic idiocy." The work of these investigators has had great influence on scientific opinion and rightly or wrongly has elevated the thymus to a position of great importance among the organs of internal secretion. During the past two years, however, some experimental work has appeared with results at variance with theirs, notably the work of Pappenheimer and Nordmann.

Pappenheimer⁹⁸ removed the thymus from rats, aged 3 weeks or less, controlling from the same litters. His original material consisted of twenty-six litters, making a total of 118 rats, eighty-three of which were thymectomized; but owing to an epidemic of dysentery his material became reduced to twenty thymectomized rats and their controls. The period of observation after operation ranged from forty-five to 131 days. Pappenheimer found that removal of the thymus does not produce disturbance in growth or development. No constant pathologic changes were found anywhere, not in any of the organs of inter-

95. Fenger, F.: On the Size and Composition of the Thymus Gland, *Jour. Biol. Chem.*, 1915, xx, 115.

96. Klose and Vogt: *Beitr. z. klin. Chir.*, 1910, p. 69.

97. Matti, H.: *Ergebn. d. inn. Med. u. Kinderh.*, 1913, x, 1.

98. Pappenheimer, A. M.: Further Experiments on the Effects of Extirpation of the Thymus in Rats, with Special Reference to the Alleged Production of Rachitic Lesions, *Jour. Exper. Med.*, 1914, xx, 477.

nal secretion. He serial sectioned the neck and thoracic tissues of his thymectomized animals for thymus rests, thus proving their absence in the twenty animals which formed the basis of his report. Since his experiments are probably the only ones in the higher mammals in which thymus rests were proved to be absent, his negative results have the value of positive experiments.

Nordmann⁹⁹ had already published two sets of thymus extirpation experiments in dogs. His latest contribution consists of the results of thymectomy experiments performed on eight litters of puppies in the second week of life. He used the operative method of von Basch, which may be called the standard for excision of the thymus, and the intratracheal insufflation of Meltzer. The puppies were fed on a mixed diet and were allowed complete freedom out of doors. He killed them at various periods after thymectomy in order to avoid the error of overlooking transitory changes. Some of them he let live for more than a year. His thymectomized dogs developed no symptoms or pathologic changes of any sort whatsoever. The necropsies revealed no thymus rests in a single instance, although a particularly careful search appears to have been made.

Nordmann's results in this set of experiments have especial importance because in his previous experiments in thymus extirpation he had obtained muscle weakness, abnormal gait with the forelegs thrown wide apart, fatigue, infections of the skin, with loss of hair, and circulatory disturbances, of which dilatation of the heart was the chief. The conclusion which he had drawn from his previous experiments was that the thymus is an important organ of internal secretion, possibly essential to life, having to do especially with the nutrition, regulation of the heart's action and resistance to infections. In the light of his recent work he now concludes that his former results were due to other causes than deprivation of thymus function, for example, infection, and that the thymus is not essential to life and its removal in young dogs is meaningless.

It should be added that Nordmann removed the spleens from several animals, as well as the thymus, without the discovery of any pathologic developments such as Klose described. One female dog deprived of both spleen and thymus bore normal puppies.

Nordmann suggests that the results of the thymectomies obtained by Matti and Klose may have been due to domestication. He charges Klose with the use of an inbred type of dog, particularly liable to the spontaneous development of rickets.

99. Nordmann, O.: Experimentelles und Klinisches über die Thymusdrüse, *Arch. f. klin. Chir.*, 1914, cvi, 172; *Deutsch. med. Wchnschr.*, 1914, xl, 1702.

100. Klose, H.: Thymusdrüse und Rachitis, *Centralbl. f. allg. Path. u. path. Anat.*, 1914, xxv, 1.

Klose,¹⁰⁰ however, has come forward with further experiments performed on goats, swine and rats, which have yielded results similar to those obtained by him previously in dogs and rabbits.

The thymus in the swine, as in other hoofed animals, is a large organ situated both in the thorax and neck, which can be removed only with difficulty and never completely (Klose). Whatever changes occur in swine or goats after operation must be, therefore, the result of partial thymectomies. Klose states that swine must be operated on between the fourth and sixth week, if symptoms of thymus deficiency are to be obtained. Signs of rachitis, such as the formation of a rachitic rosary, beading of the ribs, spontaneous fractures of the extremities and disturbances in gait, appear two to three months after the operation, but are transitory, disappearing entirely. Klose's explanation of the transitory character of the symptoms in swine is that the thymus rest which was left, completely regenerating in a short time, raises thymus function to its normal level and, consequently, causes the symptoms due to diminished function entirely to disappear. His results in goats were analogous to those in swine; in goats the thymus must be extirpated in the fourth week, if pathologic changes are to be obtained.

Klose removed the thymus from the rat on the fourteenth day. His first experiments he states were negative, or at least the ensuing changes were transitory. "Many broods behaved in a refractory manner like many kinds of dogs." Klose explained this phenomenon on the ground that thymus rests were present in the thyroid, which underwent functional hypertrophy. Many animals which were free from these rests died of cachexia on an average of from six to ten weeks after the operation and the bones of these animals showed severe grades of rickets.

Klose finds the thymus in the rat is essential to life. If an animal sufficiently young at the time of operation does not die after thymus removal, the thymus, according to Klose, cannot have been completely removed.

Klose had previously advanced the theory that the spleen was closely related in its function to the thymus and normally assumed the function of the thymus when the latter underwent physiologic involution. He explained the failure of thymectomies performed late (after the fourth week) in dogs to awaken characteristic symptoms on the supposition that the spleen had been allowed time enough to assume sufficient of the thymus' function to prevent them from developing. This theory of the interrelationship of thymus and spleen was founded largely on fancy and had already been attacked and disproved and its falsity admitted finally by Klose himself. The object of Flesch's

experiments, which are about to be described, was to investigate the relationship between the thymus and spleen.

The spleen varies in weight very considerably among normal rats, so that a difference of as much as 7 gm. in the weight of the spleens of two rats of equal body weight has no significance, even though the animals come from the same litter (Flesch). Flesch¹⁰¹ used rats, the youngest of which were four weeks old at the time of operation, and killed them from one to four weeks afterwards, or else allowed them to live until death occurred spontaneously in five to seven weeks. Each operative rat had a control.

Flesch found that complete removal of the thymus in the rat is usually impossible because of the presence of microscopic rests of the thymus in the neck, which cannot be found at the time of the operation. But he discovered that the rats having thymus rests did not react differently to a loss of the thymus from those rats in which no rests were found at the subsequent necropsy; for the rats in which cervical rests were present died spontaneously five to seven weeks after the operation, with but two operations, in one of which, when killed eighty days after the operation, an extremely large thymus rest was found, and in the other the spleen showed sufficient divergence from the normal, in Flesch's opinion, to account for the animal's survival! Flesch explained the development of symptoms in the presence of thymus rests by the conjecture that the small thymus particles which escaped removal reached a functional capacity too late to replace the main body of the thymus which had been removed. As might be expected, the thymus rests were found in the neighborhood of the parathyroids.

In this connection it is interesting to note Flesch's statement that the thymus rests sometimes showed signs of regeneration and sometimes degenerative changes. Klose, Fulci and Aschoff have maintained that a microscopic thymus rest left after incomplete thymectomy would regenerate until it reached the size of the original gland.

Flesch corroborated in the main the changes in the rat which Klose had reported. For eleven days after the operation no symptoms appeared ("latent period"); from the eleventh to the twenty-eighth day there occurred the "stage of adiposity," which was followed by the "stage of cachexia," ending in the death of the animal. But Flesch found no characteristic changes in the spleens. Enlargement of the follicles was almost always present and in the end stages an increase in amount of splenic pulp. Often, however, there was terminal sclerotic atrophy. Large cells of the megalokaryocyte type were fairly numerous. Flesch concludes that the spleen in the thymectomized animals

101. Flesch, M.: Experimentelle Thymusstudien. I. Teil. Thymus und Milz bei der Ratte, Beitr. z. klin. Chir., 1915, xcv, 376.

is in a state of increased function, which is not specific in character, but an expression of a general reaction on the part of the whole body to the loss of the thymus.

Adler¹⁰² studied the relationship between thymus function and development in the frog. He extirpated the thymus by means of the galvanocautery from 950 tadpoles, but encountered an extremely high mortality, so that the number of surviving thymectomized animals fell to thirty-two within a week of the operations, and by the end of three months, to twenty animals. At that time they were killed and examined. The thymus proved to be completely extirpated in only three frogs; in five it was found that only one lobe had been removed and in the remaining twelve frogs that portions of both lobes were still present. None of the operative animals showed abnormal growth or development. The testicles of the three thymus-free animals were larger than the testicles of the controls. The pineals and hypophyses of these three frogs showed no changes, but the thyroids showed hyperplasia, with infoldings of the epithelium and diminished colloid. Adler concluded from his experiments that an interrelationship exists in the frog between thymus and thyroid and between thymus and testis. But since his conclusions are actually based on observations in only three animals, they cannot have much value.

Tongu¹⁰³ performed thymus transplantations in dogs and rabbits. He found the most favorable place for transplantation was in the peritoneal cavity. There an autotransplant might withstand absorption for as long a period as two months. He found the thymus transplanted into the spleen, abdominal wall or subcutaneous tissues was quickly absorbed; no signs of regeneration were evident. In all of his animals he created a thymus deficiency by removal of the gland in whole or in part at the time of or prior to the transplantation. His material consisted of twenty dogs and seventy rabbits, but the number of his successful experiments was exceedingly small.

Although the most extraordinary results have been reported following transplantation of the thymus, it is now well established that even thymus autotransplants cannot escape absorption for more than a limited period of time.

Hewer¹⁰⁴ has conducted feeding experiments on rats using thymus tabloids and the dried gland. She found that large amounts of the

102. Adler, L.: *Metamorphosestudien an Batrachierlarven. I. Exstirpation endokriner Drüsen. B. Exstirpation des Thymus*, Arch. f. Entwicklungsmechn. d. Organ., 1914, xl, 1.

103. Tongu, Y.: *Recherches expérimentales sur la transplantation du thymus (Première étude)*, Mitt. a. d. Med. Fakult. d. k. Univ. zu Tokyo, 1915, xiv, 259.

104. Hewer, Evelyn: *The Effect of Thymus Feeding on the Activity of the Reproductive Organs in the Rat*, Jour. Physiol., 1914, xlvii, 479.

fresh gland were necessary to produce results and that males were more susceptible to thymus feeding than females. The feeding of both parents produced marked retardation in the sexual maturity of the offspring, but the length of the period of gestation was unchanged. If large doses of the thymus were given to the male rats, the structure of the testis was affected, degenerative changes taking place in sexually mature animals and retardation in development of the testis in animals not yet sexually mature. By giving large amounts of thymus Hewer was able to produce a condition which she calls "hyperthymism." The testes of these animals showed an absence of the Sertoli cells, and in the later stages degenerative changes in the sperm cells with diminished numbers or complete absence of spermatozoa. To produce the condition of "hyperthymism" from 2 to 5 gm. per day of thymus substance was given. No breeding took place if either the male or the female had been treated with large doses of thymus.

M'Neil¹⁰⁵ advances the hypothesis that status lymphaticus is an anaphylactic condition. He regards individuals having status lymphaticus as constitutionally anaphylactic and as reacting in an exaggerated manner to all infections. "Status lymphaticus is an abnormal condition in the body in which, if anaphylactic phenomenon occur, they do so in an exaggerated way." M'Neil furnishes no experimental evidence in favor of his hypothesis, which is pure speculation.

Paton had previously found that the testes of young guinea-pigs hypertrophied and Soli that they atrophied after thymus extirpation. Halnan and Marshall¹⁰⁶ in their turn have investigated the relation of thymus to testis in guinea-pigs and found that neither hypertrophy nor atrophy takes place after removal of the thymus. They confirmed the well-established fact that castration is followed by thymus persistence. Their thymectomized animals showed no abnormalities of growth or development, nor did removal of both thymus and testes in young guinea-pigs alter the growth of the animal up to the time of sexual maturity.

Hatai¹⁰⁷ has conducted a very painstaking investigation in the white rat of the effects of castration on the growth and the weight of certain organs, among them those of internal secretion. The most marked effect of castration on any of the organs of internal secretion was on

105. M'Neil, C.: Anaphylaxis and Status Lymphaticus: Their Relation to Intensified Types of Disease in Infancy and Childhood, *Edinburgh Med. Jour.*, 1914, New Series, xiii, 38, 120.

106. Halnan, E. T., and Marshall, F. H. A.: On the Relation Between the Thymus and the Generative Organs and the Influence of These Organs on Growth, *Proc. Roy. Soc.*, 1914, xxxviii, Series B, 68.

107. Hatai, S.: The Growth of Organs in the Albino Rat as Affected by Gonadectomy, *Jour. Exper. Zool.*, 1915, xviii, 1.

the hypophysis. No change in the weight of the hypophysis was noted after spaying or semispaying, but after castration a marked increase in weight took place. No obesity occurred in castrated animals if compensatory growth of the hypophysis had developed. Hatai noted the same tendency of the thymus to persist after castration that has been noted by other authors.

Bompiani¹⁰⁸ confirms the findings of Fulci¹⁰⁹ in regard to the capacity of the thymus to regenerate after pregnancy. Pregnancy causes the thymus to involute, but, as soon as pregnancy is interrupted, the thymus begins to regenerate. Bompiani shows in addition that lactation causes the thymus to involute, or at least keeps the thymus in a state of involution, but that as soon as lactation is stopped, regeneration makes its appearance. Many authors have described regeneration of the thymus: after Roentgen ray (Rudberg¹¹⁰) (Jonson¹¹¹); hunger (Jonson¹¹¹); pregnancy (Fulci¹¹²); partial extirpation (Friedeleben,¹¹³ Klose,¹¹⁴ Fulci,¹¹² Aschoff,¹¹⁵ etc.). Some investigators have failed to find signs of regeneration in rests left at operation (Hammar,¹¹⁶ Adler,¹¹⁷ Pappenheimer¹¹⁸ and others). The question of the behavior of the thymus after partial excision is open to further investigation.

During the past two years Hammar has made at least three contributions to the subject of thymus pathology. The first paper¹¹⁹ cannot be located and therefore is not included in this review.

The first of the two available papers of Hammar's¹²⁰ is a critical study of fourteen thymus glands taken from cases in which the diag-

108. Bompiani, G.: Der Einfluss des Säugens auf die Restitutionsfähigkeit des Thymus nach der Schwangerschaft (Vorläufige Mitteilung), *Centralbl. f. allg. Path. u. path. Anat.*, 1914, 929; L'influenza dell'allattamento sulla capacità di reintegrazione del timo dopo la gravidanza, *Gazz. internaz. di med.*, 1915, xviii, 65.

109. Fulci, F.: *Centralbl. f. allg. Path. u. path. Anat.*, 1913, xxiv, 968.

110. Rudberg: *Arch. f. Anat.*, 1907, 123; *On Thymus Involutionen* Diss., Upsala, 1910.

111. Jonson: *Arch. f. mikroskop. Anat.*, 1909, lxxiii, 390.

112. Fulci, F.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 1776.

113. Friedeleben: *Die Physiologie der Thymusdrüse in Gesundheit und Krankheit vom Standpunkte experimenteller Erforschung und klinischer Erfahrung*, Frankfurt, 1858.

114. Klose: *Neue Deutsche Chirurgie*, Enke, Stuttgart, 1912.

115. Aschoff: *Tr. Internat. Cong. Med.*, 1913, Lond.; 1914, Sect. iii, *Gen Path. and Path. Anat.*, Part 2, 131.

116. Hammar, J. A.: *Arch. f. d. ges. Physiol.*, cx.

117. Adler: *Arch. f. Entwicklungsmechn. d. Organ*, 1914, xi, 1.

118. Pappenheimer: *Jour. Exper. Med.*, 1914, xx, 477.

119. Hammar himself refers to this article, *Mikroskopische Analyse der Thymus in 21 Fällen Basedowscher Krankheit*, *Beitr. z. klin. Chir.*, 1915, but it is not in that journal.

120. Hammar, J. A.: *Mikroskopische Analyse der Thymus in 14 Fällen sogenannten Thymustodes*, *Ztschr. f. Kinderh.*, 1916, xiii, 153.

nosis of "thymus death" was made, with the special object of determining the truth or falsity of certain of the existing beliefs in regard to the pathologic changes in the thymus in that condition.

For full exposition of the opinions of various writers on the subject of the pathology of the thymus in status lymphaticus the reader is referred to Hammar's original article. Suffice it here to point out that certain pathologists have taken the position that the hyperplastic thymus, or more particularly the thymus of "thymus death," presents typical pathologic changes, consisting in (1) an altered relation of medulla to cortex, (2) a change in the number, size and histologic characters of the Hassall corpuscles, and (3) the composition of the medulla. Hedinger in 1906 directed attention to the occurrence, in cases of "thymus death," of a broad medullary and narrow cortical zone, and Schridde¹²¹ writes that the most important feature of the hyperplastic thymus is hyperplasia of the medulla, with hypoplasia of the cortex, and further, that the Hassall bodies are almost always exceedingly large and composed of fat-containing protoplasm without nuclei. In the more recent edition of Aschoff's book (1911) Schridde distinguishes two types of hyperplastic thymus, one in which medulla and cortex are both hyperplastic; the other, far the commoner of the two, in which medulla is hyperplastic and cortex hypoplastic. The hyperplasia of the medulla is characterized by an actual increase of the reticular cells (the undoubted epithelial element) and by the presence of large forms of Hassall corpuscles, though the total number per unit of thymus substance is diminished. In regard to the thymus of "thymus death," Schridde states specifically that, excepting those rare cases in which the thymus operates mechanically, hyperplasia of the medulla and hypoplasia of the cortex are invariably present. While not entirely accepting Schridde's conclusions, Hart finds medullary hypertrophy and considers the cause to be an active proliferation of the epithelial cells. His views in regard to the excessive production of Hassall corpuscles in conditions of excessive function of the thymus have already been discussed. Though other writers (Wiesel, Pappenheimer and others) have expressed dissenting opinions, nevertheless the dogmatic teachings of the Schridde school have received wide acceptance and are frequently quoted in the experimental literature on the thymus gland (Matti, Klose¹²² and others). It is the truth or falsity of these views which Hammar seeks to investigate.

121. Schridde: Aschoff's Pathology, Ed. 1.

122. As Hammar points out, the description which Klose gives of the pathologic changes in the thymus of status lymphaticus is Schridde's description almost word for word. See *Neue Deutsche Chirurgie der Thymusdrüse*, p. 113.

Before taking up Hammar's paper, however, it is necessary to call attention to the special methods of study used by him in this investigation, which gives to his results a mathematical accuracy. The exact amount of parenchyma (minus the fat and connective tissue) he was enabled to estimate by means of serial sections and reconstructions and in the same manner to determine the exact relation of medullary to cortical substance.¹²³ The Hassall corpuscles he counted.

At the beginning of his paper Hammar points out that although it is popularly supposed that the enlargement of the thymus in "*mors thymica*" is constant, statistics prove that such is by no means the case, for the weight of the thymus may be normal or even subnormal in that condition. Thirteen of Hammar's series of fourteen thymus glands were taken from children whose ages ranged between 9 days and 16 years. The remaining gland was that of an adult. Of the thirteen children's glands, only two were enlarged; the others showed amounts of parenchyma within normal limits. The two enlarged thymus glands had increased amounts of cortex; the medulla in one was larger than normal, though not in proportion to the cortex, and in the other lay within normal limits. The cortico-medullary index (cortical tissue, medullary tissue) was, therefore, high in both instances. (A high cortical medullary index is normal for childhood.) Both thymus glands showed subnormal numbers of Hassall's corpuscles; the very large and calcified forms were absent. A lymphatic infiltration of the medulla was present in both. Of the eleven thymus glands of normal size, one showed signs of accidental involution and was excluded from further consideration. In the remaining ten glands there was diminished parenchyma in all and a high cortico-medullary index in six. The very large and the calcified Hassall corpuscles were also absent in all. Infiltration of the medulla with lymphocytes was found in eight. In no two of the ten glands were all the characters enumerated the same.

The study of these thirteen glands showed it was not possible to distinguish any fixed type and, in fact, in the majority of the glands the variations were within normal limits. There seemed to be no morphologic ground on which to rest a theory of hyperfunction or dysfunction.

Hammar's second paper is an analysis of the mechanical theory of thymic asthma in the light of the study of the form and topographical relations of the thymus gland. Grawitz in 1888 put forward the idea that it was possible for the thymus to become wedged between the

123. Hammar, J. A.: *Methode, die Menge der Rinde und des Marks des Thymus, sowie die Anzahl und Grösse der Hassallschen Körper zahlenmässig festzustellen* (unter besonderer Berücksichtigung der Verhältnisse beim Menschen), *Ztschr. f. ang. Anat.*, 1913-1914, i, 311.

upper part of the sternum and the vertebral column in such a way as to compress the trachea at that point, causing death from asphyxia. The space between the upper portion of the manubrium and spine has been known ever since Grawitz's publication as "the critical space of Grawitz." Since then other investigators (Barack,¹²⁴ Strassmann, Flügge¹²⁵) have described a second vulnerable spot, where the trachea may be compressed by the hyperplastic thymus, namely, the point of crossing of the innominate artery. Hart, Wiesel, Klose and others recognize these two points as the places where compression of the trachea by the enlarged thymus is particularly liable to occur.

A considerable number of cases of thymic asthma have been described in the literature, chiefly by surgeons, in which the surgical operation or necropsy demonstrated a large thymus or even a causal relationship between the enlarged thymus and the clinical or pathologic condition. The one most prominent symptom reported in these cases has been inspiratory dyspnea with inspiratory stridor, though in some of them expiratory dyspnea was also referred to. The points of compression of the trachea were thought to be at the "critical points" already mentioned. The inspiratory dyspnea in "thymic asthma" has been explained by assuming that the thymus acts like a ball valve, being forced against the trachea at one of the two "critical points" during inspiration, in such a way as to compress it, but falling away again during expiration, permitting the trachea to expand once more. Surgeons who have operated on these patients with "thymic asthma" have observed that the inspiratory dyspnea ceased when the thymus was drawn upward into the neck, but recurred as soon as the thymus was allowed to resume its former position in the thorax; or that the inspiratory dyspnea was permanently diminished when the thymus was drawn upward into the neck and held in that position by suture of the capsule to the sternum.

Hammar's paper shows, in the first place, that the two so-called "critical points" at which it is thought the trachea may be compressed by the thymus are so close to each other, particularly in the new-born child, as to be almost identical, for the innominate artery crosses the trachea close to the upper border of the sternum. Therefore, it is useless to consider them separately. The statement that the trachea was greatly compressed immediately above the bifurcation where the innominate artery crosses is erroneous, for the innominate artery lies considerably above the bifurcation. If the trachea was actually compressed at that point by the thymus, that part of the thymus lying immediately opposite, just above the base of the heart, must have been

124. Barack: Diss. Berlin, 1894; cited by Hammar.

125. Flügge: Vierteljahrsschr. f. gerichtl. u. öffentl. Med., Sanitätswesen, 1899, Series 3, xvii; cited by Hammar.

responsible. The next point which Hammar makes is that since the thickest portion of the thymus lies at the level of the base of the heart, considerably below the so-called "critical point," the surgical maneuver of drawing the thymus upward not only could not possibly relieve dyspnea produced by pressure of the thymus on the trachea at the critical points, but would actually intensify it, since it would bring a thicker mass of thymus between the top of the sternum and the spine than was there previously. If the ascent of the thymus relieved the inspiratory dyspnea of "thymic asthma," it was proof that the point of compression of the trachea did not lie above the thickest portion of the thymus, but at or below the thickest part, in the neighborhood of the bifurcation. In reality the thymus is not forced upward into the neck with each inspiration, but recedes into the thorax, while it is during expiration that it is forced up into the base of the neck ("Rehn's phenomenon"), so that if it produced dyspnea by compression of the trachea anywhere above its thickest part, it would cause expiratory and not inspiratory dyspnea.

Thus Hammar proves that the existing notions about the mechanical compression of the trachea by the enlarged thymus are largely false. He points out, however, that his anatomical preparations indicate the enlarged thymus may exert pressure on the trachea close to the bifurcation, or on the bronchi, particularly in the new-born child, whose thymus is relatively much broader than at a later period. Hammar is careful to avoid the statement that the thymus does actually compress the trachea at these points.

It is to Hammar's painstaking investigations in regard to the thymus, which have never been shown to be wrong in a single particular, that we owe the greater part of our certain knowledge in regard to that organ. The results of his analysis of the fourteen thymus glands from cases of thymus death are probably worth more than the opinions of all those pathologists who have expressed themselves so positively on this subject, because the latter have dealt with impressions, while Hammar has worked out the facts. It is probable that there is no pathologic condition which is characteristic for the thymus of "thymic death" or status lymphaticus. Hammar makes ridiculous the controversionalists who have split hairs on the subject of the compression of the trachea by the enlarged thymus at the "critical points."

THE THYROID

Halstead¹²⁶ showed by experiments performed in 1887 and 1888 that after excision of a portion of the dog's thyroid the remainder underwent hypertrophy.

126. Halstead, W. S.: Johns Hopkins Hosp. Reports, 1896, i, 373.

Hunnicut¹²⁷ has repeated Halstead's experiments at Halstead's own suggestion. He removed the thyroid piecemeal from thirty-nine dogs and found that in only one of them did the thyroid rest develop hyperplasia. In twenty other dogs, similarly treated, the wounds were left open to determine whether a relationship existed between hyperplasia of the thyroid and infection; but no hyperplasia resulted. Hunnicutt found that one entire lobe and three-fourths of the other lobe of the dog's thyroid could be removed without affecting the remainder of the gland. In only three of the total fifty-nine animals in which piecemeal removal of the thyroid was done did the remaining piece of gland change from the normal to the hyperplastic state, while in five of the fifty-nine dogs the thyroid, which had been found to be hyperplastic in the first place, reverted back in the interval to the normal state, that is, the thyroid rest at the conclusion of the experiment proved to be normal. Definite increase in the size of the rest was not discovered in any instance.

Hunnicut¹²⁷ calls attention to the great variability in the histologic structure of the thyroid of the dog. Sections taken from the thyroids before any operation had been performed showed marked hyperplasia in 32 per cent. of the animals and early signs of hyperplasia in 5 per cent. No partially thyroidectomized dog developed myxedema or tetany.

On the other hand, Basinger, who removed the thyroids from rabbits in order to produce myxedema, found that thyroid rests have a great tendency to undergo hyperplasia. "Care was taken to remove all thyroid tissue, because it is surprising how often small remnants of tissue were hypertrophic." The remnants were never more than one-tenth of the size of one of the lobes of the thyroid.

Douglas¹²⁸ examined the thyroids of pigeons, fowls, rats and rabbits to determine the extent of normal variation in the histologic structure of the thyroid in different members of the same species. He concluded that the histologic picture of the thyroid in different animals of the same species kept under the same conditions is so variable that an interpretation of experimental results based on histologic changes in the thyroid is extremely difficult.

Fox¹²⁹ reports marked variations in the thyroids of wild animals confined in the zoological garden in Philadelphia.

127. Hunnicutt, J. A.: The Absence of Hyperplasia of the Remainder of the Thyroid in Dogs After Piecemeal Removal of This Gland; Autotransplantation of the Thyroid in Partially Thyroidectomized Animals, *Am. Jour. Med. Sc.*, 1914, cxlviii, 207. Halstead, W. S.: *Ibid.*, cxlvii, 56.

128. Douglas, M.: The Histology of the Thyroid in Animals Fed on Various Diets, *Jour. Path. and Bacteriol.*, 1914-1915, xix, 341.

129. Fox, H.: The Pathology of the Thyroid Gland in Wild Animals, *Proc. Path. Soc. Philadelphia*, 1915, New Series, xvii, 20.

McCarrison¹³⁰ has made comparative studies of the thyroid gland of wild rats, of white rats and mice kept in confinement and of goitrous rats, both wild and domestic. It was his observation that goiter was exceedingly rare in wild rats, but that the structure of the thyroid gland varied within wide limits and appeared to be especially influenced by altitude and season. A larger proportion of thyroids of domesticated white rats were in a state of active secretion than was the case with the thyroids of wild rats. A small proportion of white rats confined in cages developed goiter spontaneously.

Jackson investigated the effects of starvation on the thyroids of rats. He found that when young rats were held for several weeks, on a diet just sufficient for maintenance, histologic changes appeared in the thyroid; the follicular epithelium became atrophied and reduced in height, the nuclei hypochromatic and pycnotic, and in extreme cases, fragmented; the cytoplasm was more affected than the nucleus, but in some instances showed no changes, while in others it was vacuolated; the colloid appeared normal in some instances, in others disintegrated and replaced by desquamated epithelial cells. The changes just described Jackson thinks in no wise typical of hunger effects, but such as are seen in the thyroid in numerous pathologic conditions.

Jackson found also that the thyroid of the albino rat lost but little weight in acute inanition of sufficient degree to cause the body as a whole a loss of one-third of its total weight. In chronic inanition, on the other hand, the thyroid lost from 22 to 24 per cent. of its weight.

Bensley¹³² also comments on the variability of the structure of the thyroid in animals and the frequency of environmental changes:

The readiness with which the thyroid gland undergoes hyperplastic changes, its responsiveness to iodine administration, as demonstrated by Marine and his co-workers, the ease by which it may be modified structurally by dietary conditions, as shown by the work of Reid Hunt (1911), Marine, Chalmers, Watson (1907), Tanberg (1900) and Missiroli (1910), and confirmed by my recent studies on the relation of diet to hyperplasia in opossums under domestication, confirm the conclusion that there is a delicate adjustment between the functioning of the thyroid gland and general body conditions, though at present we do not know the means by which this adjustment is mediated.

In 1914 Gudernatsch¹³³ reported the results of his second series of feeding experiments on tadpoles. He found that when tadpoles were

130. McCarrison, R.: Nervous Cretinism, *Brit. Jour. Child. Dis.*, 1914, x1, 508.

131. Jackson, C. M.: Effect of Acute and Chronic Inanition on the Relative Weights of the Various Organs and Systems of Adult Albino Rats, *Anat. Rec.*, 1915, ix, 90.

132. Bensley, R. R.: The Normal Mode of Secretion in the Thyroid Gland, *Am. Jour. Anat.*, 1916, xix, 37.

133. Gudernatsch, J. F.: Feeding Experiments on Tadpoles. II. A Further Contribution to the Knowledge of Organs with Internal Secretion, *Am. Jour. Anat.*, 1914, xv, 431.

fed large amounts of thyroid, they emaciated rapidly and died, but when fed the proper amounts, remained alive and metamorphosed into frogs on the eighteenth day, although normally the tadpole does not turn into the frog until from 10 to 13 weeks old. The result of the premature transition of tadpole to frog was that frogs in miniature were produced, but which never ate, and died within a few days to several weeks. On the other hand, Gudernatsch found that tadpoles fed thymus or spleen grew rapidly, but showed no tendency to metamorphose into frogs. Not one of several thousands of tadpoles fed on thymus could be made to develop into a frog, though tadpoles fed on liver became frogs at the normal period. Gudernatsch, therefore, concluded that the thyroid contained some substance which specifically stimulated development (differentiation in the frog), accelerating it, but at the same time inhibiting growth, while the thymus contained some substance which accelerated growth but inhibited development, also in a specific manner, and that this substance was likewise contained in the spleen and probably also in lymphatic tissue, though to a less extent than in the thymus. The results of Gudernatsch's experiments were confirmed by Romeis¹³⁴ (Stettner).

Morse¹³⁵ undertook to determine the element in the thyroid gland which caused the changes in growth and development of the tadpole described by Gudernatsch. He excluded the lipoid of the thyroid as the possible substance by obtaining the same effects in the tadpole with lipoid-free thyroid as with untreated thyroid. He next obtained negative results with "metallic" iodine, potassium iodide, methyl iodide, iodobenzoic acid, etc., showing that inorganic iodine is not the substance in question. Iodine-bearing algae, used to determine the effect of iodine in organic combination, and starch iodate ("colloidal iodine such as exists in starch") were both without effect. Kurajeff's blood protein iodine compound ("iodalbin") was effective, however, and both thyroid derivatives, thyroglobulin and iodothyronine, gave results indistinguishable from those produced by thyroid itself. Iodized amino-acids produced less pronounced yet positive results. Morse concludes that the substance in the thyroid which produces the specific effect "concerns the iodine, which is associated in some way with the amino-acids composing the complex iodized globulin of the thyroid." He explains the effectiveness of the iodized blood albumin by its protein linkage.

134. Romeis, B.: Experimentelle Untersuchungen über die Wirkung innersekretorischer Organe. II. Der Einfluss von Thyreoidea- und Thymusfütterung auf das Wachstum, die Entwicklung und die Regeneration von Anurenlarven, Arch. f. Entwicklungsmech. d. Organ., 1914, xxxvii, 571; Ibid., xl, 571; Ibid., xli, 57.

135. Morse, M.: The Effective Principle in Thyroid Accelerating Involution in Frog Larvae, Jour. Biol. Chem., 1914, xix, 421.

Lenhart¹³⁶ also studied the effects of thyroid feeding on tadpoles. He gave the experimental tadpoles on alternate days desiccated thyroid taken from sheep, cattle and man (goiter cases), together with fresh pig liver, while he fed the latter substance daily without admixture of thyroid to the control tadpoles. The idea underlying the experiments was to determine whether the iodine element of the thyroid was the substance which produced the characteristic changes in the tadpoles. Accordingly, Lenhart estimated the iodine content of the thyroid powder in each instance before use. The results of Lenhart's feeding experiments were similar to those of Gudernatsch: large amounts of thyroid caused the tadpoles to emaciate and die before differentiation commenced, but smaller amounts caused differentiation to occur earlier. But Lenhart offered a different interpretation for the results obtained from that of Gudernatsch, namely, that thyroid feeding produced merely an acceleration of the normal metabolism of the tadpole, which in turn manifested itself by a more rapid development and so an earlier metamorphosis.

Like Morse, Lenhart found that nonthyroid iodine, for example, potassium iodide, produced no effect on the tadpole. The effectiveness of the thyroid feeding was, however, always in direct proportion to its iodine content, so that Lenhart concluded the iodine element in the thyroid is the active principle responsible for the changes obtained. No different effect was discovered when the human thyroid was used; if anything, human thyroid was not so potent as the thyroid of the dog.

Stettner¹³⁷ has investigated the effects on tadpoles of feeding thymus, thyroid and genital tissue (ovaries and testes). The thyroid-fed tadpoles were affected exactly like those of Gudernatsch and Lenhart. The thymus-fed tadpoles showed marked irregularities in growth and development. They tended to metamorphose late and develop into malformed frogs with short legs, large abdomens and well-developed musculature. Growth in the majority of the thymus-fed tadpoles appeared to be slightly retarded, but some, receiving extract from a particular thymus (that of a young female calf), attained a giant size. Genital gland feeding produced, in most instances, a late metamorphosis, into a thin frog with slender muscles. The combination of thymus and genital feedings caused metamorphosis at its normal time and led to the production of a normally formed frog.

136. Lenhart, C. H.: The Influence on Tadpoles of Feeding Desiccated Thyroid Gland in Variable Amounts and of Variable Iodine Contents, *Jour. Exper. Med.*, 1915, xxii, 739.

137. Stettner, E.: Beeinflussung des Wachstums von Kaulquappen durch Verfütterung von Thymus und geschlechtsorganen, *Jahrb. f. Kinderh.*, 1916, lxxxiii, 154.

Stettner saw in the results of his experiments the specific effects of the organs of internal secretion. In his opinion the experiments showed that thymus and genital gland acted in an antagonistic manner and a proper admixture of both was necessary for perfect development, for, though either one given singly caused a retardation in development, their effects were the opposite in other respects. He thought it possible that the deformities of the thymus-fed tadpoles might be rachitic.

The results of the feeding experiments of Gudernatsch, Romeis, Morse, Lenhart and Stettner make certain the effects of thyroid feeding on tadpoles. But the effects of thymus feeding have not been shown so clearly. Though Gudernatsch found that thymus feeding postponed indefinitely metamorphosis in the tadpole, he obtained similar results with splenic tissue, which indicates that the effect of thymus feeding, though definite, was not specific, or at least the active substance was not limited to the thymus, and Stettner's results, which were not exactly like those of Gudernatsch, were not sufficiently uniform to permit of any definite interpretation. The exact effect of thymus feeding on the tadpole should be determined by new, suitably controlled experiments.

Basinger's¹³⁸ experiments, already referred to in connection with the question of thyroid hyperplasia, were undertaken with the view of establishing a biologic test for the active principle of the thyroid, but were actually concerned with the determination of the effects of normal rabbit blood serum, "hyperthyroid" blood serum, standard thyroid preparations, thyroid metaprotein and Kendall's extract B on cretinized rabbits.

He was able to produce cretin rabbits in about eighty-one out of a total of 140 animals. He found certain litters more refractory than others: for example, he succeeded in obtaining cretins in 90 per cent. of some of the litters operated on, while in others in only 25 per cent. The symptoms of experimental cretinism in the rabbit corresponded to the clinical picture of cretinism in human beings. About two weeks after the extirpation of the thyroid the hair became drier, inclined to stand up and could be pulled out easily. In the third week after operation retardation in growth became noticeable. By the tenth week the average weight of the cretin rabbits was 750 gm., while that of the control rabbits was 1,400 gm. The bones showed a "pseudorickety condition" called by Hofmeister "chondrodystrophia thyreopriva" (Basinger). Still later the cretin rabbits developed potbellies and scaly eczematous-like lesions of the skin. They became slow and

138. Basinger, H. R.: The Control of Experimental Cretinism, *THE ARCHIVES INT. MED.*, xvii, 260.

awkward in their movements and would sit for hours without moving. Sixteen cretin rabbits Basinger kept alive for more than one year.

Normal blood serum transfusions produced no effect on the cretin rabbits. But the blood serum of rabbits fed on thyroid to the point of hyperthyroidism did cause definite improvement, but less than that caused by thyroid feeding. The cretin rabbits, which were fed thyroid the moment symptoms appeared, never grew quite so large as the control rabbits, although the other signs of cretinism disappeared. Kendall's thyroid extract B had no effect. A further interesting point, which Basinger's experiments brought out, was that the cretin rabbits continued to grow after the period when growth of the normal rabbits had ceased.

During the past few years the treatment of cretinism and myxedema by thyroid transplantation has been attempted in several of the European clinics, notably in those of Kocher, Payr and Eiselberg. The transference of thyroid tissue from one individual to another is simple; the difficulty lies in making the transplanted tissue live and functionate. If this difficulty can be surmounted, the cure of cretinism and myxedema can be accomplished, instead of the approximation to complete cure afforded by oral thyroid therapy. Hence the great importance of the attempts to treat cretinism by means of thyroid implantation.

Payr points out that almost all the transplantation work on the thyroid in animals has been done with autotransplants and probably many of the poor results of thyroid transplantation in human beings have been due to the necessity of using homeotransplants. Very little experimental work in homeotransplantation of the thyroid has been done, but as the knowledge about tissue transplantation increases, tissue specificity is becoming more apparent and the number of tissues which permit of homeotransplantation is becoming correspondingly less. Payr believes the outlook for successful transplantation is more hopeful in cases in which the thyroid is deficient than in those in which the thyroid is absent. The best results, he thinks, are obtained by the use of homeotransplants from blood relatives. He advises the use of a large piece of thyroid as a transplant, rather than a small piece or several small pieces. The best sites for the transplants are probably the spleen or thymus, the latter on account of its accessibility. There are undoubtedly cases, he thinks, in which transplantation of the thyroid brought about a favorable result, when oral therapy had failed, and a few cases in which the effect of the transplantation could be followed for years. Payr states that the therapeutic effect from

139. Payr, E.: Zur Frage der Schilddrüsentransplantation, *Arch. f. klin. Chir.*, 1914, cvi, 16.

thyroid transplantation is more rapid and complete than from thyroid feeding, probably because more elements are present in the internal secretion of the thyroid than can be absorbed through the intestinal tract.

Payr concludes his article with the report of five of his own cases. One of his patients, an eight-year-old cretin, received in the spleen a large piece of her mother's thyroid. In the succeeding half-year she grew 12 cm., when in the three previous years she had grown only 6 cm. and her development in other respects was commensurate with her growth. Two and a third years after the transplantation the patient had a recrudescence of her myxedema, so that the results of the thyroid transplantation were not permanent. Payr's other cases were much less striking than the case just described.

Von Eiselsberg¹⁴⁰ reported two cases of cretinism in which he had transplanted thyroid. In a 13-year-old cretin he had made altogether six implantations of pieces of human thyroid obtained as chance offered. The favorable results following transplantation were only temporary. The other patient was similarly given three thyroid grafts and improved during a short period of observation. Von Eiselsberg also calls attention to the *éclatant* effects produced by transplantation as compared with feeding, the former being much more rapid in their development than the latter.

Kocher¹⁴¹ has contributed his experiences in the treatment of myxedematous conditions by means of thyroid transplantation. The main points in his paper are the following: In no case has a complete and permanent restitution to the normal condition been accomplished in a myxedematous human subject as a result of thyroid transplantation, but in some cases definite improvement has followed, as evidenced by the fact that a smaller amount of thyroid extract was required by the patient, or that the patient himself was conscious of feeling better. He states that before making the transplantation it is necessary to give the patient a preliminary treatment with thyroid, not to make certain of the diagnosis, but to raise the patient's tissues to such a level of nutrition as to enable them to nourish the transplant after it has been received and that the donor must have an active or hyperactive thyroid. Kocher plants either a single large piece of thyroid or a number of smaller pieces and immediately after the transplantation continues the thyroid therapy by mouth in order to combat "thyroid hunger."¹⁴²

140. Von Eiselsberg, A. F.: Zur Frage der dauernden Einheilung verpflanzter Schilddrüsen und Nebenschilddrüsen, zugleich ein Beitrag zur post-operativen Tetania parathyreopriva, Arch. f. klin. Chir., 1914, cvi, 1.

141. Kocher, T.: Ueber die Bedingungen erfolgreicher Schilddrüsentransplantation beim Menschen, Arch. f. klin. Chir., 1914, cv, 832.

142. For a discussion of the most favorable sites for the transplants consult Kocher's article (Footnote 141).

Eighteen of Kocher's patients appear to have been improved by the thyroid transplantation, while in the eighteen other patients no improvement of any kind resulted.

The experimental literature in regard to thyroid transplantation, as Payr points out, relates almost entirely to autoplasmic transplantation (von Eiselsberg,¹⁴³ 1892; Enderlen,¹⁴⁴ 1898; Payr,¹⁴⁵ 1906; Salzer,¹⁴⁶ 1909; Cristiani). Cristiani,¹⁴⁷ who between the years 1894 and 1906 wrote thirty papers on the subject of thyroid transplantation, is the only investigator mentioning homeotransplantation (Hesselberg).

Hesselberg's¹⁴⁸ work bears immediately on this subject and consists of the direct comparison of the growth and development of thyroid homeo- and autotransplants. Her material was guinea-pigs, numbering in all seventy-five animals. Autotransplantation and homeotransplantation were performed simultaneously in pairs of animals, so that direct comparison was possible. The experimental animals were killed at various periods after transplantation and the transplanted tissues excised and sectioned. For a short time after the operation no differences in the transplants were observed. Comparatively soon, however, a destruction of the follicles of the homeotransplants was noticeable, due apparently to an invasion of lymphocytes and an ingrowth of connective tissue. The latter grew much more abundantly into the homeotransplants than into the autotransplants, remaining cellular in the latter, while it became fibrous in the former. The autotransplants developed far the better blood supply. At the end of forty-seven days the homeotransplants had practically disappeared, while the autotransplants were not only living, but showed signs of outgrowth into the surrounding tissue.

Whether homeotransplantation of the thyroid is a success or a failure when applied to human beings with thyroid deficiency cannot be answered with certainty until the fate of the transplanted human thyroid is known. Hesselberg's experiments demonstrate that in the guinea-pig the thyroid tissue transplanted from another individual survives only for a short time. The results of the homeotransplantation experiments in myxedematous human subjects, just

143. Von Eiselsberg: *Wien. klin. Wchnschr.*, 1892, v, 81.

144. Enderlen: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1898, iii, 474.

145. Payr: *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1906, xxxv, 503; *Arch. f. klin. Chir.*, 1906, lxxx, 730.

146. Salzer: *Arch. f. klin. Chir.*, 1909, lxxxix, 881.

147. Cristiani: For a list of his very numerous publications on this subject, see bibliography at end of article by Hesselberg, Cora: A Comparison of Autoplasmic and Homeoplasmic Transplantation of Thyroid Tissue in the Guinea-Pig. *Jour. Exper. Med.*, 1915, xxi, 164.

148. Citation given in Footnote 147.

related, point also to the same conclusion. The treatment of cretinism by thyroid transplantation up to the present time must be considered a failure and in all probability will never succeed until the problem of the overcoming of tissue specificity is solved.

Fenger¹⁴⁹ found that both enlarged and normal-sized human fetal thyroids contain iodine, at least during the last three months of fetal life, as do the thyroids of cattle, swine and sheep. Because the fetal thyroid contains iodine, Fenger assumes that it functionates in fetal life.

The observation was made a long time ago that the thymus is frequently enlarged in exophthalmic goiter, even in poorly nourished adult subjects whose thymus glands under normal conditions are atrophied. In 1858 Markham¹⁵⁰ reported a case of exophthalmic goiter showing large thymus at necropsy and Moebius¹⁵¹ discussed the significance of enlarged thymus in exophthalmic goiter in his well-known monograph on that subject. But the statistical studies of the past few years, in particular those of Thorbecke¹⁵² and Capelle¹⁵³ have shown an incidence of large thymus in exophthalmic goiter previously unsuspected. For example, Capelle's figures revealed an enlargement or persistence of the thymus in 95 per cent. of fatal cases of exophthalmic goiter and in 44 per cent. dying from other causes. Since the coincidence of large thymus and exophthalmic goiter is too frequent to be explained as accidental, the question naturally arose whether the thymus might not be actively concerned in the production of exophthalmic goiter. The possibility that this might be so was strengthened by the experimental investigations of Matti⁹⁷ and Klose,⁹⁶ which indicated, as already pointed out, that the thymus is itself one of the most important of the organs of internal secretion and that a definite interrelationship exists between thyroid and thymus in that the thyroid becomes hyperplastic when the thymus is extirpated. Still further evidence in support of a thymogenic influence in exophthalmic goiter has been supplied by surgeons, who, acting on the theory that the thymus exerted a deleterious influence, have treated patients by excision of a portion of the thymus, as well as the thyroid, or by partial excision of the thymus alone.

Numerous reports that reduction of both thymus and thyroid have caused more favorable results than those obtained from partial thy-

149. Fenger, F.: On the Presence of Iodine in the Human Fetal Thyroid Gland, *Jour. Biol. Chem.*, 1915, xx, 695.

150. Markham: *Med. Times and Gaz.*, May 1, 1858; cited by Hart.

151. Moebius: *Deutsch. Ztschr. f. Nervenhe.*, 1891, i, 5; Nothnagel: *Spec. Pathol. u. Therapie Bas'sche Krankh.*, Wien., 1896.

152. Thorbecke, M.: *Der Morbus Basedow mit Thymus persistenz*, Diss., Heidelberg, 1905; cited by Capelle.

153. Capelle: *Beitr. z. klin. Chir.*, 1908, lviii, 353.

roidectomy alone have appeared in the literature (Garrè,¹⁵⁴ von Haberer,¹⁵⁵ Klose,¹⁵⁶ Sauerbruch¹⁵⁷ and others). In two recent papers von Haberer¹⁵⁸ reports good results in a series of cases of exophthalmic goiter treated by reduction of both organs, and Halstead the beneficial effects of the Roentgen-ray treatment of the thymus in several cases of exophthalmic goiter in which the thyroids had been partially resected without much improvement. But more important with a view to the determination of the part actually played by the thymus in exophthalmic goiter are the cases treated by the excision of thymus alone, of which there are now a number in the literature (Garrè, von Haberer, Capelle and Bayer, Sauerbruch and others). Although the results in these cases of thymus resection alone are reported as favorable, in no instance has the operation been curative, and in at least two of the cases a subsequent partial excision of the thyroid was necessary. Not one of them proves that the thymus can cause exophthalmic goiter, and in fact none furnishes convincing proof that the thymus has anything whatsoever to do with the production of that disease. Nevertheless, Hart and others regard the proof established, chiefly from their interpretation of the results in these cases, that a purely thymogenic form of exophthalmic goiter exists. Hart recognizes three types of exophthalmic goiter, (1) purely thyrogenic, (2) purely thymogenic, and (3) a mixed form, though he admits that the purely thymogenic form is rare. Klose, as usual, takes the extreme position "no thymus, no Basedow."

Two hypotheses have been advanced to explain the rôle the thymus plays in exophthalmic goiter. According to one of them, that advanced by Gebele,¹⁵⁹ the thymus is thought to compensate for the thyroid insufficiency and for that reason to hypertrophy or at least to persist when the thyroid function becomes sufficiently affected; in other words, the thyroid is the primary cause of exophthalmic goiter and the thymus plays a secondary part. According to the other hypothesis, that of Capelle and Bayer,¹⁶⁰ and accepted by Klose,¹⁶¹ Hart and others, the thymus is thought to have an independent pathologic function, which adds to or intensifies the symptoms produced by the diseased

154. Garrè: *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1911, No. 1.

155. Von Haberer: *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1913, No. 1.

156. Klose: *Berl. klin. Wchnschr.*, 1914, No. 1.

157. Sauerbruch: *Beitr. z. klin. Chir.*, 1912, lxxvii.

158. Von Haberer, H.: *Kasuistisches zur Frage therapeutischer Misserfolge bei Morbus Basedowii*, *Wien. klin. Wchnschr.*, 1915, xxviii, 1; *Over de klinische beteekenis der thymusklier (special met't oog op den Morbus Basedowii en den status thymicus)*, *Med. Weekbl.*, 1914-1915, xxi, 242.

159. Gebele: *Beitr. z. klin. Chir.*, 1910, lxx, No. 1; *Ibid.*, 1911, lxxvi.

160. Capelle, W., and Bayer, R.: *Beitr. z. klin. Chir.*, 1913, lxxxvi, 509.

161. Klose: Footnote 156; Lampé Liesegang: *Beitr. z. klin. Chir.*, lxxvii.

thyroid; that is, the thyroid and thymus share in the production of exophthalmic goiter.

Various pathologic changes in the thymus of exophthalmic goiter have been described, but none of them are constant. It is probably true that no pathologic condition of the thymus characteristic of exophthalmic goiter exists.

Von Haberer¹⁵⁸ states in a recent paper on this subject that results of the treatment of exophthalmic goiter by partial excision of the thymus have failed to show that a purely thymogenic form exists, although they indicate that the thymus exerts an important pathologic influence. He admits that it is not feasible to distinguish the symptoms produced by the thymus and thyroid. The effect in exophthalmic goiter of thymus reduction, in addition to thyroidectomy, is to make the subsequent course more favorable. Undoubtedly cases of exophthalmic goiter exist in which the thymus plays no part.

In the more recent of his two papers on this subject von Haberer¹⁵⁸ reports two more patients with exophthalmic goiter treated by the combined operation on thymus and thyroid. One of the cases had a fatal termination soon after the operation, with the extreme post-operative tachycardia now so commonly regarded as due to pathologic thymus function. Although the occurrence in this case of symptoms referable to the thymus, after a large part of the latter had been removed, appeared to speak against the theory of thymic influence in exophthalmic goiter, the necropsy, according to von Haberer, tended to strengthen the theory, since it revealed 70 gm. of thymus tissue still remaining in the thorax.

Albert Kocher's¹⁶² paper deals with this same subject. The main points brought out are the following: Exophthalmic goiter without hyperplasia of the thyroid is unknown. On the other hand, numerous cases of exophthalmic goiter with a normal thymus have been established. The thymus undergoes late hyperplasia or revivescence in from 45 to 50 per cent. of the cases of exophthalmic goiter. Its enlargement is much commoner in young than in old subjects. The histologic picture of the thymus shows nothing characteristic to distinguish it from the hyperplasia of childhood. Thymus hyperplasia is much commoner in certain neighborhoods and in certain families than in others. If the thyroid is sufficiently reduced, thymus hyperplasia decreases. The operation for reduction of the thyroid is no more dangerous when enlargement of the thymus exists than when no enlargement is present. If the symptoms of exophthalmic goiter are obstinate, with a tendency to exacerbation, part of the thymus may be removed in addition to the

162. Kocher, A.: Ueber Basedow'sche Krankheit und Thymus, *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1914, xliii, Part 2, p. 567.

thyroid. A pretreatment with thymus preparations or Roentgen ray may be tried, if the cases are found to react favorably to them.

Klaus¹⁶³ reports a case of exophthalmic goiter occurring in a child 9 months old. The evidences of the disease were exophthalmos, noticed by the parents in the third week, well-marked von Graefe's and Stellwag's signs, and a palpable thyroid, thought to be enlarged. The thymus was judged to be considerably enlarged because of an increase in perimanubrial dulness. The child was known to have rickets and tuberculosis. He was given a single tuberculin treatment and was not seen again for a year. But, when examined again, at the end of that time, he showed no signs at all of exophthalmic goiter; the exophthalmos and the enlargement of the thyroid were gone. Klaus reports the case as the earliest instance of exophthalmic goiter on record.

Inasmuch as exophthalmos occurs in anemic, rachitic children quite independently of exophthalmic goiter; and von Graefe's sign is occasionally seen in normal infants, and slightly enlarged thyroids in infants do not necessarily have a pathologic significance; and the size of the thymus cannot surely be determined by percussion, the case can scarcely be accepted as one of exophthalmic goiter, at least on the data furnished by Klaus. The additional fact that all signs of the disease had disappeared spontaneously after a year makes the correctness of Klaus' diagnosis still more doubtful.

The review of the literature on the thyroid cannot close without mention of the experiments of Cannon and his co-workers. In the past two years these investigators have developed at least two new methods of study of the endocrine glands, which may have far-reaching results. They furnish also the first physiologic proof of hormonal interaction between two organs of internal secretion, the suprarenal and thyroid. Their experiments are among the most brilliant that have ever been done in this field of investigation.

Cannon, Binger and Fitz¹⁶⁴ have produced the symptoms of hyperthyroidism in cats by anastomosing the anterior root of the right phrenic nerve to the right cervical sympathetic, so that, after regeneration had taken place, the thyroid might receive a stimulation with each respiration. The six cats that were alive five months after the anastomosis had been performed showed tachycardia, diarrhea, increased excitability and accelerated metabolism. One of the cats developed exophthalmos. In the cat most affected the suprarenals were found to

163. Klaus, O.: Basedow bei einem neun Monate alten Kinde, *Prag. med. Wchnschr.*, 1914, xxxix, 515.

164. Cannon, W. B., Binger, C. A. L., and Fitz, R.: Experimental Hyperthyroidism, *Am. Jour. Physiol.*, 1914-1915, xxxvi, 363.

be three times their normal weight. In a recent paper Cannon and Fitz have shown that the symptoms just mentioned could be made to disappear by removing the thyroid on the side on which the anastomosis of phrenic and sympathetic had been originally performed.

Cannon and Cattell¹⁶⁵ confirmed the observation of Bayliss and Bradford, made in 1885, that an electrical change in the submaxillary gland accompanies the act of secretion and that the change is absent when secretion is not taking place. Applying the same method of investigation to the ductless glands, they found that an action current was set up in the thyroid when the sympathetic was stimulated, and similarly an action current in the suprarenal followed stimulation of the splanchnic nerve. The latent period after stimulation of both thyroid and suprarenal was considerably longer than that which followed stimulation of the salivary glands.

Applying this method of study to the thyroid gland,¹⁶⁶ they found again that stimulation of the sympathetic trunk in the thorax produced an action current in the thyroid gland, which did not occur when other nerves were stimulated; and that this action current remained after the superior and inferior laryngeal nerves had been cut. When the cervical sympathetic was cut, the action current still persisted though in a modified form, but disappeared entirely when the inferior cervical ganglion also was removed. Stimulation of the vagus produced no action current. Cannon and Cattell offer these experiments as proof of the sympathetic innervation of the thyroid gland. Anatomists have already traced fibers from the cervical sympathetic to the thyroid, and previous investigators have shown that atrophy of the thyroid follows severance of its cervical sympathetic nerves (Cannon and Cattell).

Cannon and Cattell¹⁶⁷ have also succeeded in experimentally demonstrating an interrelationship between suprarenal and thyroid. They first showed that the injection of small doses of epinephrin into the blood stream of the cat induced an action current in the thyroid. Stimulation of the splanchnic nerve, physiologically separated from the central nervous system, likewise invoked an action current in the thyroid. The action current did not occur, however, after stimulation of the splanchnic if the return of blood from the abdomen was prevented, but took place promptly when the pent-up blood was released.

165. Cannon, W. B., and Cattell, McK.: Some Results of Studies on Electrical Changes in Glands, *Am. Jour. Physiol.*, 1916, xl, 143.

166. Cannon, W. B., and Cattell, McK.: Some Conditions Controlling Thyroid Activity, *Boston Med. and Surg. Jour.*, 1916, clxxiv, 138.

167. Cannon, W. B., and Cattell, McK.: III. Influence of Suprarenal Secretion on Thyroid, *Am. Jour. Physiol.*, 1916, xli, 74.

The electrical change also failed to appear after splanchnic stimulation if the suprarenal glands had been previously removed.

"GLANDULA INSULARIS CERVICALIS": A NEW ORGAN OF INTERNAL
SECRETION

Pende¹⁶⁸ describes a structure found in the neck of man, the dog and other animals in the last months of intrauterine life and during the first year, but not after that time, which he thinks is a hitherto unnoticed organ of internal secretion. It is made up of numerous small lobular masses, scattered about in the neighborhood of the thymus and thyroid, and especially likely to be present near the upper pole of the thymus or close to the parathyroids. Some of the separate masses are large enough to be seen with the naked eye as grayish, red particles. The total volume of the "gland" is greater than that of the parathyroids. The lobules, which are sharply separated from each other, are composed of epithelial cells, which are larger in some instances, in others smaller, than the cells of the parathyroids. The cytoplasm contains an abundance of basophilic and acidophilic granules, vacuoles and lipoid substances, while the nuclei are large and round, or in some instances small and pale staining. No connective tissue stroma is present.

Pende's reasons for thinking the structure is an endocrine gland are based solely on histologic appearances. The cells impress him as being epithelial and secretory.

It is thought that Pende's new organ of internal secretion is embryonal fat tissue. Its scattered and irregular distribution, its complete disappearance soon after birth and the comparison of the illustrations in Pende's article with sections of embryonic fat from the necks of new-born puppies makes this suggestion highly probable. Dr. Milton Winternitz¹⁶⁹ first expressed this view.

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OBSTETRIC PARALYSIS

ITS ETIOLOGY, PATHOLOGY, CLINICAL ASPECTS AND TREATMENT, WITH
A REPORT OF FOUR HUNDRED AND SEVENTY CASES *

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Obstetric paralysis, a paralysis produced during birth, is due to an injury to the nerves of the brachial plexus. The resultant paralysis is characteristic; the arm hangs vertically, the elbow extended, the forearm pronated and the whole arm inwardly rotated. The paralysis is usually flaccid.

I shall endeavor in this paper, by a review of all the literature, to give the reader the various theories as to the causes of the paralysis, as well as to offer the conclusions I have reached by a study of 470 cases. Certain experimental work which I have done, with the idea of determining clearly the etiology and pathology, will be described and conclusions drawn therefrom. The pathologic and clinical aspects of the condition will be discussed and analyzed, and the treatment, operative and nonoperative, will be dealt with under appropriate headings. Definite conclusions will be drawn from the study of about 500 cases, which will show conclusively that traction on the brachial plexus, and a resultant injury of the plexus, is the one cause of the condition.

Up to within a year or so most of us were reasonably content to accept the theory that the paralysis in these cases was due to a stretching or tearing of some of the roots of the brachial plexus, due to a forcible separation of the head and shoulders during labor. Other theories have been discussed and have been given some credence, but recently a new one has appeared. It seems that it is about time for us to take an account of stock and see which of these various ideas which have been advanced are reasonable and based on pathologic findings and clinical facts.

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Obstetric paralysis was first described by Smellie¹ in 1768, who believed the condition due to long pressure on the arm while the child was in the pelvis; but it was first brought prominently to the notice of the medical profession in 1872 by Duchenne, who described four cases in infants and attributed the condition to pressure of forceps or fingers in the axilla on the nerve trunks.

Duchenne¹ recognized that the lesion might occur in obstetric operations, such as disengaging the upraised arm in a breech or footling presentation, in delivering after version, or in making traction on the arm of the child after the birth of the head, and quotes cases to support this theory. These procedures result in direct traction on the cords of the plexus, and when force is used probably cause injuries to the nerves. It was not until 1874 that Erb¹ described the same type of paralysis in adults, since which time it has been commonly known as the Erb-Duchenne paralysis. Erb showed that pressure above the shoulder on the junction of the fifth and sixth cervical nerve roots, the so-called Erb's point, caused the characteristic grouping of the paralyzed muscles. He laid the occurrence of the paralysis especially "to the energetic application of the so-called Prague grip (Fig. 1), in which the fingers are applied like a fork over the back of the child's neck, with an after-coming head, and so endangering the integrity of the brachial plexus by energetic traction and compression.

Stransky,¹ in a most careful review of the whole literature up to 1902, presents the subject in detail and most conclusively. He reviews Smellie (1768), Danyau (1851), Guéniot (1867), and Depauls' work, the latter cited by Seeligmuller. He reports ninety-four cases from various authors whose works he has reviewed. Stransky believed that pressure as well as hard pulling in some cases was an adequate cause, especially if ether had been used and the child was asphyxiated. The following authors are quoted from Stransky's article:

Seeligmuller thought that pressure from forceps often caused hemorrhage about the plexus. Thorburn (1886) reported a case of lower arm paralysis, and believed the tearing of the nerves to be due to hyperextension of the shoulder as the arm was drawn above the head, but also ascribed it to pressure of the clavicle on Erb's point from the bad position of the arm.

Roulland (1884) gave all the various positions in which the condition could occur, and apparently believed it due to direct or indirect pressure on the plexus. Arens (1889) believed it due to hemorrhage or tearing of the nerves.

1. Stransky: *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.*, July, 1902, p. 497, with complete bibliography to date, 1902.

Küstner* (1888) advanced a theory that has been rejected at once by all other writers who have had any extensive experience with the cases, namely, that the trouble is usually due to a fracture of bones or separation of the humeral epiphysis.

Danchez (1891) believed the condition to be spontaneous, from pressure on the circumflex nerve of the arm while the child was caught in the pelvis, or that it might be traumatic from finger or instrumental pressure. He also believed that when the lower arm was



Fig. 1.—The delivery of the after-coming head, with the occiput posterior, by means of the Prague grip (Kerr).

involved the condition was one of "pseudoparalysis," as also did D'Astros (1892), that is, not a paralysis from nerve injury, but an arm held motionless on account of bruising and consequent pain, or as the result of bone injury. Gowers believed the paralysis to be due to pressure from forceps, and Weil (1896) that it was due to trauma, especially with an after-coming head. Peter thought it due to pressure of the forceps or strong lateral bending of the head, with a delayed

shoulder, or turning of the head in breech cases. Guilleminot (1896) likewise supported the theory that the condition was due to compression of forceps or a strong pull; and Jolly (1896) believed it due to pressure, chiefly with an after-coming head.

Stransky quotes the experimental work of Fieux (1896), Schoemaker (1899), Stolper (1901), Küstner (1888), and Landold, as follows:

Fieux opposed Erb's views, in that Erb's point was too small and that the pressure would have to be too sharply localized, so that on the whole the theory that finger pressure or forceps could produce it was unlikely. Pressure of finger he also rejects, for there was nothing for the finger to compress the plexus against. He comes finally to traction on the upper roots as the longest side of the triangle formed by the cords of the plexus, with lateral inclination of the head, as tending to increase the distance between the head and shoulder. He produced the paralysis in rabbits by pulling the head forcibly to one side. He showed that the amount of separation which occurred between the ends of the cut roots of the brachial plexus, when the shoulder was held down and the head carried to the opposite side with as much force as is used in ordinary labors, is as follows: The two upper cords, or fifth and sixth cervical, separated from 26 to 28 mm., the third, or seventh cervical, only 12 mm., and the lower two, the eighth cervical and first dorsal, only 8 mm. The point at which the rupture occurs is from a quarter to half an inch from the point of emergence from the spinal canal near the junction of the fifth and sixth cervical roots. Fibers of the suprascapular nerve always ruptured among the first.

Schoemaker also conducted experiments on cadavers with the plexus exposed, and could always tear the fifth and sixth cervical, but never the seventh and eighth. He also thought that the clavicle could cause pressure on the plexus by having it caught between the clavicle and first rib and spine. He was opposed to the theory that pressure from the fingers caused the injury. Küstner (second paper) and Landold also did experimental work and believed the injury due to traction. Stolper agreed in the main with Fieux and Schoemaker, but rejected the possibility of pressure on the plexus in breech cases, and believed that clavicular pressure might cause the paralysis. However, he believed that stretching was the main factor.

Taking up now other authors, some of whom published their articles previous to 1902, and are quoted by Stransky, I will give comprehensive abstracts from their original articles.

Lovett² (1892) reports nine cases and discussed the conditions of

2. Lovett, R. W.: *The Surgical Aspect of the Paralysis of New-Born Children*, Boston Med. and Surg. Jour., July 7, 1892.

the labor, most of which were long, hard and instrumental. He believes that the paralysis is due to some direct injury to the brachial plexus and is generally associated with strong traction made on the head. Out of nine cases, four had the right arm affected, four the left and one case was not noted.

Carter³ (1893) believed strongly that overstretching of the cords of the brachial plexus is the cause of the paralysis. He reported sixteen cases of his own, with an analysis of the conditions at labor, besides comparing his cases and observations with those reported by Lovett² and Burr. He believed that in a left occipito-anterior position the right arm would be the one affected, and in right occipito-anterior position the left arm would be the one to be injured. Nine of his own cases showed paralysis on the right and seven on the left. Burr's cases (quoted by Lovett) showed the right arm involved nine times in nine cases, regardless of position. Carter also discusses the factors of pressure of forceps on the plexus, the hook, and the finger pressing directly on the plexus in the neck, pressure of the finger in the axilla and overextension of the arm. He does not believe that these factors are essential in the production of the paralysis.

Walton⁴ (1896) states that "neither the seat of the lesion nor the method of its production has been absolutely determined, but that the preponderance of evidence appears to establish the brachial plexus rather than the spinal cord as the point of injury." He discusses the relations of the position of the fetus to the paralysis of the right or left arm, and reaches about the same conclusion as Carter, except that he believes that the injury to the plexus is brought about by pressure on the plexus by its being caught between the upper edge of the clavicle and the first rib. He believes that a more careful study should be made of the positions and presentations of these children so as to determine the definite mechanics of the injury. He believes that the suprascapular nerve is independently stretched in the separation of the head from the shoulder, the distal point of fixation being either the suprascapular notch or the outer edge of the scapular spine, around which the nerve immediately passes, or both.

Haynes⁵ (1897) reports three cases. He quotes Starr, who says:

It is the pressure of the obstetrician's fingers which causes the injury in the majority of cases, and I have noticed that in 75 per cent. of the cases seen the paralysis was in the left arm, which finds its explanation in the greater

3. Carter, C. F.: *Obstetrical Paralysis, with Reference Especially to the Pathology and Etiology*. Boston Med. and Surg. Jour., 1893, cxxxviii, No. 18.

4. Walton, G. L.: *The Etiology of Obstetrical Paralysis*, Boston Med. and Surg. Jour., Dec. 24, 1896.

5. Haynes, W. H.: *Obstetrical Paralysis of Infants*, Brooklyn Med. Jour., May, 1897.

length of the middle finger of the hand which is doing the damage. In the act of traction there is a tendency of the obstetrician to flex the fingers, and then the tip of the finger is pressed deeply into the side of the child's neck.

This is very interesting, but hardly scientific. Haynes presents no new ideas on the subject.

Robinson⁶ (1899) reports seventeen cases, in only one of which was birth reported as normal. All the others had a definite history of the labor being tedious and difficult. In eleven the presentation was cranial; in three special mention was made of difficulty in delivering the arms; four others had forceps applied. He states that J. E. Simpson has shown that the heads of boys are larger than the heads of girls, and therefore the heads of the latter would not dilate the way for the shoulders as well as the former. In his own series thirteen babies out of seventeen were girls, which would bear out this theory that there was an insufficiently dilated canal for the shoulders and that they therefore caught, or were with difficulty delivered, and in so doing there was a strain put on the cords of the plexus.

J. J. Thomas⁷ (1905), Warrington and Jones⁸ (1896) and Stone⁹ (1900) believed the paralysis to be due to overstretching of the nerves of the plexus at birth, and Thomas reports two cases of bilateral paralysis of the lower arm type, following difficult labors with face presentation, in which he believed the injury to be the result of excessive lordosis or hyperextension in the face position, a view also concurred in by Jolly.

Bullard¹⁰ (1907) likewise believes that overstretching of the nerve trunks is the cause of the paralysis, and that traction on the head in the axis of the body is less injurious than when the traction is made obliquely so that the head is inclined to one side when the traction is made. Rotation of the head to the opposite side also stretches the nerves. This is a factor which Walton also considers of the greatest importance. Firm resistance should be offered in order to have the force effective on the nerves, which may be supplied by a shoulder caught behind the pubes or by an after-coming head in a breech delivery (Fig. 2). Asphyxia is also a favorable condition, in that, with the child in that condition, all muscles are fully relaxed and

6. Robinson, H. B.: Traumatic Birth Paralysis of the Upper Extremity. St. Thomas Hospital Reports, 1899, xxvi.

7. Thomas, J. J.: Two Cases of Bilateral Birth Paralysis of the Lower Arm Type, with bibliography, Boston Med. and Surg. Jour., Oct. 19, 1905, cliii, No. 16.

8. Warrington and Jones: Observations on Paralysis of the Brachial Plexus. Lancet, London, Dec. 15, 1906.

9. Stone, J. S.: Injuries about the Shoulder Joint at Birth, Boston Med. and Surg. Jour., March 8, 1900, cxlii, No. 11.

10. Bullard, W. N.: Obstetric Paralysis, Am. Jour. Med. Sc., July, 1907.

their resistance is absent. Under this condition the nerves, without their usual support and protection, are more easily torn. He found that the cases generally occurred when the labor was long and difficult, when instruments were used in abnormal presentations, especially breech, and when the child was asphyxiated. In regard to the position of the occiput, it has been stated that in a left occipito-anterior position the right arm would be the one paralyzed, as the right shoulder would be the one caught behind the pubes; but this was not borne out by the few observations he was able to make, for in seventeen



Fig. 2.—Stretching of nerves by oblique traction when the shoulder is caught under the pubes.

cases of left occipito-anterior position eight of the infants were paralyzed on the right and nine on the left.

Taylor¹¹ (1907) states that the cause of brachial birth palsy is due to tension or overstretching of the nerves of the brachial plexus. This he has confirmed by numerous dissections and experiments on infantile cadavers. The overstretching was caused by forcible separa-

11. Taylor, A. S.: Results from the Surgical Treatment of Brachial Birth Palsy, *Jour. Am. Med. Assn.*, 1907, *xlvi*, 96.

tion of the head and shoulders in vertex presentation by pulling on the head, and in breech presentation by pulling on the shoulder, by the so-called Prague method (Fig. 1). He reports the delivery of a breech case when he felt the roots of the plexus tear under his fingers, which was later confirmed by necropsy.

Osterhaus¹² (1908) likewise believes the injury to be due to overstretching.

Bailey¹³ (1908) believes the condition concerns the obstetrician more than it does any other practitioner. He states that while pressure is the generally accepted cause, he is of the opinion that overstretching and traction on the plexus is the real one. He states that



Fig. 3.—Stretching of nerves by oblique traction in delivering the posterior shoulder when caught on the perineum (Bumm).

if the axis of the head is drawn away from the long axis of the body by 30 degrees, the cords of the plexus are drawn to the danger point. This is liable to happen in vertex presentations to hasten the delivery of the shoulder, and in breech presentations to hasten the delivery of the after-coming head. It may also happen in extraction by forceps.

12. Osterhaus, Karl: *Obstetrical Paralysis*, New York Med. Jour., Nov. 7, 1908.

13. Bailey, P.: *Brachial Birth Palsy*, Bull. Lying-In Hosp., New York, March, 1908.

and in spontaneous birth the delivered head by its own weight may cause traction on the plexus (Figs. 3 and 4).

Frazier and Skillern¹⁴ (1911) speak of the older theory that the brachial plexus injuries were caused by the plexus being crushed or squeezed between the clavicle and first rib, or transverse processes of the cervical vertebrae. Subsequent observations, however, have proved that in all cases the essential element in the causation is traction on the nerves.



Fig. 4.—Separation of head and shoulder, with shoulder caught behind the pubes (Nagel).

Lange¹⁵ (1912) believes the paralysis is due to a tearing of the capsule of the shoulder joint, which at first limits motion because of pain and then from habit. He was the first to suggest the theory which T. T. Thomas has taken up, that the condition is purely secondary to a shoulder joint injury. It should rightly be called Lange's theory.

14. Frazier and Skillern: Suprascapular Subcutaneous Lesions of the Brachial Plexus Not Associated with Skeletal Injuries, *Jour. Am. Med. Assn.*, 1911, lvii, 1957.

15. Lange: *München. med. Wchnschr.*, No. 26, 1912.

Frauenthal¹⁶ (1912) believes also in the overstretching theory and reports cases, but is rather optimistic as to his results.

T. T. Thomas¹⁷ (1914), in an interesting theoretical discussion of the problem, based on a study of nine cases averaging 6.5 years, concludes that the paralysis is secondary to a primary traumatic dislocation of the shoulder occurring at birth, associated with a tear in the joint capsule and a consequent involvement of the plexus in the exudate, practically Lange's theory, as given above. He does not explain why the exudate always avoids the major portion of the plexus in the region of the shoulder joint, or why it practically always works its way at least two inches above the clavicle and picks out the junction of

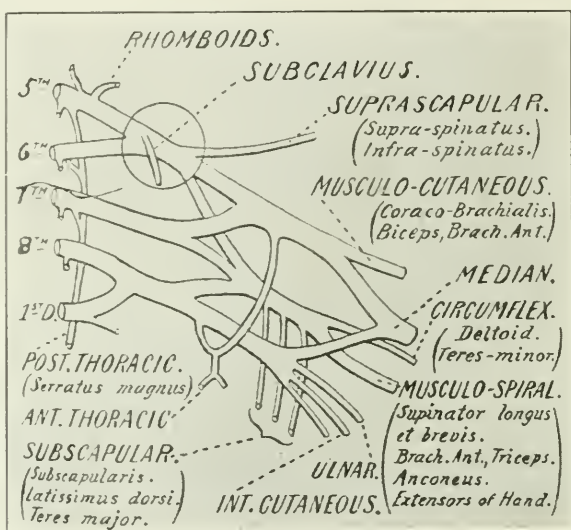


Fig. 5.—Brachial plexus, showing Erb's point. The subscapular nerve in this illustration comes off below Erb's point, but generally arises from the fifth nerve above its junction with the sixth cervical root.

the fifth and sixth cervical nerves to produce the characteristic paralysis. This theory of his, which is purely philosophical, is ingenious, but not reasonable, nor is it based on clinical or pathologic evidence. Erb's point is small and it requires definite injury at this point to produce the characteristic paralysis, as well as injury above this point on the fifth cervical root to produce the paralysis of the supraspinatus and infraspinatus from trauma to the suprascapular nerve which comes off the fifth cervical just above or below Erb's point (Fig. 5).

16. Frauenthal: Erb's Palsy, Am. Jour. Obst., 1912, lxx, No. 4.

17. Thomas, T. T.: The Relation of Posterior Subluxations of the Shoulder Joint to Obstetrical Palsy of the Upper Extremity, Ann. Surg., 1914.

Fairbank¹⁸ (1913) is another believer in the traction theory, and he reports forty cases, thirty-two of which were vertex presentations and seven breech, which rather refutes Tubby and Sherren, whom he quotes and who believe that it occurs equally in the two presentations. He also states that long, difficult labors, in which forceps were used, predisposed to the injury (Figs. 6, 7 and 8).

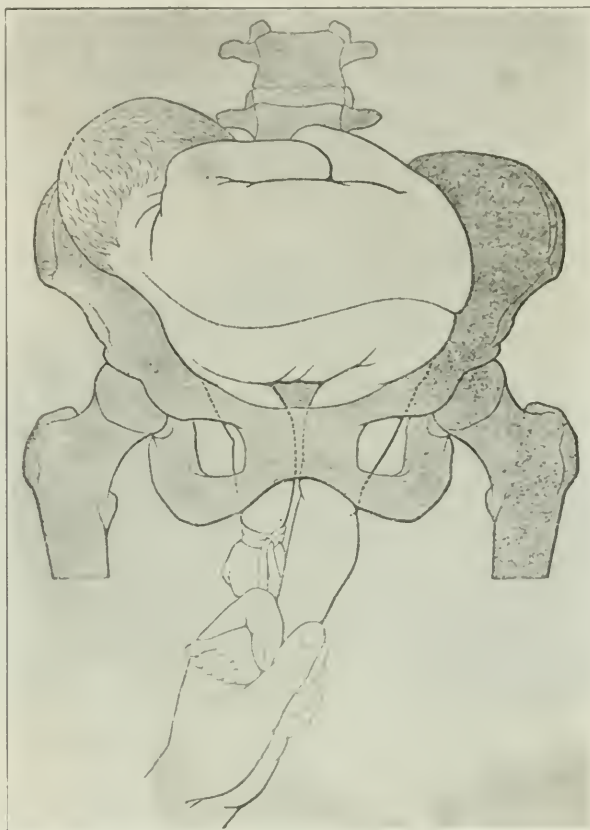


Fig. 6.—Version in dorso-anterior position, first stage; a difficult labor, predisposing to injury (Faraboeuf and Varnier).

Peltesohn¹⁹ (1914) has found a number of cases which he reports as “false birth palsies.” He describes typical end-results of cases of obstetric paralysis. He states that the condition is due to injury of the upper epiphysis of the humerus at birth. In true Erb’s paralysis there is no disturbance of the epiphysis.

18. Fairbank, H. A. T.: Birth Palsy; Subluxation of the Shoulder Joint in Infants and Young Children, *Lancet*, London, May 3, 1913.

19. Peltesohn, S.: Injuries of the Upper End of the Humerus in Birth Palsies, *Berl. klin. Wchnschr.*, June 22, 1914, p. 1162.

Gaugele²⁰ (1914) states that so-called obstetric paralysis is not a true paralysis, and the cause of the condition is an injury to the capsule and soft parts with subsequent contraction. Injury to the epiphysis or other injury is not uncommon. He evidently bases his conclusion on the study of four cases, and is not familiar with the work of other observers.

Van Neck²¹ (1914) believes that other conditions than injury to the plexus may simulate obstetric paralysis, such as epiphyseal injuries of the head of the humerus, congenital developmental errors of the plexus, and shoulder turning resulting in a tear of the capsule. These all present definite clinical pictures, and by Roentgen ray and careful clinical examinations the diagnosis should be made easy and not confused with obstetric paralysis.

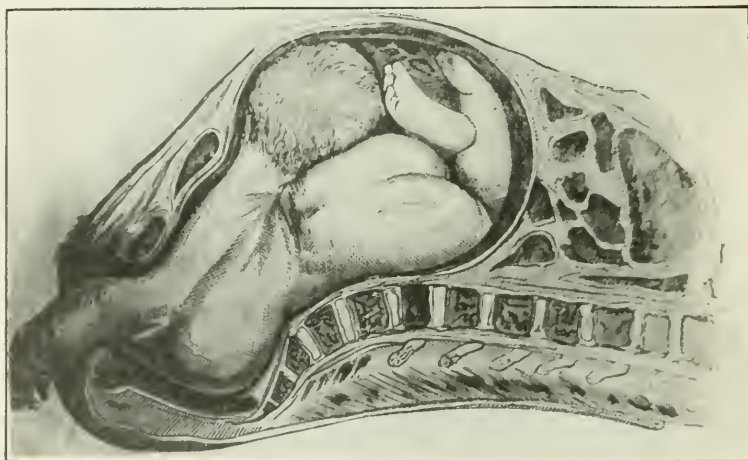


Fig. 7.—Neglected shoulder presentation; section through frozen corpse; a difficult labor, predisposing to injury (Chiara).

Gordon²² (1914) believes also in the traction theory, as well as the theories of direct pressure on the plexus by the obstetrician's finger, the hook, and pressure by the clavicle and transverse processes.

Platt²³ (1915) is also a follower of the traction theory, and bases his ideas on five cases. He quotes other authors, including Lange and Vulpinus, the former believing in the laceration of the capsule theory

20. Gaugele, K.: So-Called Obstetrical Paralysis of the Arm, *Ztschr. f. orthop. Chir.*, 1914, xxxvi, Nos. 3 and 4.

21. Van Neck: Congenital or Obstetrical Lesions of the Shoulder and Brachial Plexus, *Jour. méd. de Bruxelles*, 1914, No. 11.

22. Gordon, A.: An Unusual Form of Birth Palsy, *Jour. Am. Med. Assn.*, 1914, lxiii, 2282.

23. Platt, H.: Birth Palsy, *Brit. Med. Jour.*, May 8, 1915.

and the latter in the theory of epiphyseal displacement as causes of the paralysis and subsequent deformity.

Darling²⁴ (1915), in an extensive study of the various lesions of the brachial plexus and a discussion of the various theories, accepts the ones based on definite nerve findings and pathology, and believes that traction on the cords of the brachial plexus is the generally accepted one in view of clinical and experimental evidence.



Fig. 8.—Forcible separation of head and shoulder in a shoulder presentation, putting the plexus on a stretch, which is almost sure to result in injury to the nerves (Kleinwächter).

Sharpe²⁵ (1916) has demonstrated that direct injury of the nerves always occurs, as shown by operation on the plexus in fifty-six cases;

24. Darling, H. C. R.: *Med. Jour. Australia*, Oct. 9, 1915.

25. Sharpe, W.: *The Operative Treatment of Brachial Plexus Paralysis*, *Jour. Am. Med. Assn.*, 1916, lxvi, 876.

in every case finding definite pathologic evidence of injury. He believes the injury is caused by overstretching of the plexus at birth, due generally to a prolonged, forcible separation of the head and shoulder by lateral extension during a difficult labor.

This rather hasty review of practically all the literature on this subject from the etiologic point of view shows that the majority of observers incline toward the traction theory, which is in turn definitely supported by pathologic and clinical evidence. It is not questioned that fracture and epiphyseal displacement occur, and that they may be associated with an injury to the brachial plexus as a separate entity, but that they are the one cause of the usual type of birth palsy cannot be accepted. I have seen a number of cases of fracture of the upper end of the humerus occurring at birth which simulated brachial palsy, but on careful study were properly diagnosed. The after-course was quite different from that seen in brachial plexus injuries.

PATHOLOGY

There are generally two well-recognized types of paralysis seen. The more common one consists of a lesion which involves the fifth and sixth cervical roots and the suprascapular nerve and produces a paralysis of only the muscles of the upper arm, with the exception of the supinators. This type is known as the upper arm type. The less usual type, the so-called lower arm, a whole arm type, is the result of injury not only to the fifth and sixth cervical roots, but the seventh and eighth and possibly the first thoracic as well. Here the whole arm is flaccid; there is a wrist-drop and paralysis of the small muscles of the hand. There rarely occurs the pure lower arm type of paralysis without any involvement of the upper cords of the plexus, the so-called Klumpke's paralysis, several cases having been reported by J. J. Thomas, Jolly, Guillemot, Seeligmuller, Thorburn, Raymond, Comby and Danchez. These cases show a paralysis usually the result of stretching of the plexus from overextension of the head in cases of face presentation, and due to injury to the lower cords of the plexus, namely, the seventh and eighth cervical roots. They may at times be bilateral. It is in this type that one often sees inequality of the pupils, owing to the fact that the sympathetic fibers from the deep cervical ganglionic plexus enter the spinal cord through the first dorsal and at times through the eighth cervical roots. Injury therefore to these roots leads to an unopposed action of the motor oculi nerve.

Pathologically, in the milder cases the stretching or tearing forces result in a greater or less degree of hemorrhage or edema into the nerve sheaths. In others there may be a rupture of the perineural sheath, accompanied by hemorrhage into the substances of the nerve trunk, associated with a tearing apart or separation of the nerve fibers.

TABLE 1.—AUTHORS WHO HAVE REPORTED CASES, THE DATES OF THEIR REPORTS AND NUMBER OF CASES REPORTED

Authors	Date	Number Cases Reported	Authors	Date	Number Cases Reported
Duchenne.....	1872	4	Schoemaker.....	1899	2
Nadaud.....	1872	3	Haslinger.....	1899	2
Erb.....	1874	2	Bollenhagen.....	1899	1
Duecounneau.....	1876	2	Robinson.....	1899	17
Seeligmuller.....	1877-1882	8	Steiner.....	1900	1
Roulland.....	1884	1	Thomas, H. M.	1900	3
Thorburn.....	1886	1	Maygrier.....	1901	1
Arens.....	1889	1	Stolper.....	1901	1
Henoch.....	1890	1	Peter, cited by Stransky.	1902	2
Danchez.....	1891	1	Oppenheim, cited by Stransky.	1902	1
Cited by Danchez:			Koster, cited by Stransky.....	1902	4
Budin.....	1	Schultze, cited by Stransky.....	1902	1
Babinski.....	1	Thomas, J. J.	1905	2
Monnier.....	..	2	Bullard*.....	1907†	178
Burr.....	1892	8	Murphy.....	1907	1
Lovett.....	1892	9	Taylor, A. S.	1908	10
D'Astros.....	1892	1	Osterhaus.....	1908	2
Bailly and Onimus, cited by D'Astros.....	..	1	Rhode.....	1909	1
Comby, cited by D'Astros.....	1	Frauenthal... ..	1912	4
Carter.....	1893	16	Fairbank.....	1913	40
Hochstetter.....	1893	1	Lange.....	1913	17
Weil.....	1896	1	Thomas, T. T.	1913	9
Fioux.....	1896-7	2	Peltesohn.....	1914	5
Jolly.....	1896-7	3	Gaugele.....	1914	4
Guillemot.....	1896	12	Gordon.....	1914	1
Walton.....	1896	2	Van Neck.....	1914	3
Haynes.....	1897	3	Platt.....	1915	5
Warrington and Jones... ..	1896	2	Sharpe.....	1916	56
Cibert.....	1897	2			
Plauchu.....	1898	1			
Fifty-eight authors. Total number of cases reported to date 457. Number of cases reported in this paper.....					470

* The Bullard cases are included in this paper, which actually gives a total of reported cases of from 279 to 470.

† Forty-three in detail.

This latter condition leads, of course, to permanently impaired function and the formation of scar tissue in the nerve track. In the more severe cases of the upper arm type there is a partial or complete division of the fifth and sixth cervical roots, which leads to a more permanent form of paralysis than usual, and the formation of a more extensive area of scar tissue.

The force producing these lesions is variable and so the lesions are variable. The nerve roots are often frayed out inside the sheath instead of being torn across evenly, and in this way the lesion may be incomplete at any given cross section of a nerve, but involves different fibers at different levels. This scar tissue contracts in time, and not only effectually prevents the regeneration of the nerves, but may by its contraction press on and destroy the few fibers which may have escaped the original injury.

When there has been a complete or partial evulsion of the fifth and sixth cervical nerves from the spinal cord the condition pathologically is as follows: The spinal meninges over the affected area are thickened, fibrous and adherent to the cord. The affected side of the spinal cord is smaller than normal, and the injured areas of the cord may be invaded by the scar tissue. The anterior horns may be more or less disturbed, with a reduction in the number of the cells, which show various stages of degeneration; adjacent nerve tracks are more or less damaged. The anterior and posterior roots, as well as the brachial plexus on the affected side, are smaller than normal. Changes also take place in the cerebrum analogous to those found after amputation, such as a reduction of the Betz cells and a gross lesion of the fibers in the motor, intermediate and precentral area (Robinson⁶).

The other type, known as the lower arm or whole arm type, is the result of either a lesion involving all the nerves of the plexus, or, in the distinctly lower arm type, in which the lower arm and hand are alone involved, the so-called Klumpke's paralysis, in which the lesion probably involves the eighth cervical and first dorsal roots alone. This type generally results from traction applied in a breech case with the arm extended, or to traction in the axilla in a vertex presentation. It may be seen also in adults, when the first dorsal root is overstretched, as evidenced by some of the cases reported by T. T. Thomas.¹⁷ Pathologically, the conditions are similar to those seen in the other types, depending on the severity of the injury. No case in which operation has been performed has failed to show a definite pathologic lesion of the brachial plexus, definitely corresponding to the muscles involved.

Danyau (quoted by Stransky¹) in 1851 showed by necropsy that the nerves of the plexus had been torn and were surrounded and

invaded by scar tissue. Boyer²⁶ also reports necropsy findings, and states that the "opposite side of the spinal cord was distorted and otherwise altered by the injury and resulting fibrotic changes." Practically all observers, especially those who have operated in these cases, have found definite changes in the plexus due to injury and scar tissue formation. Among these, for detailed study, may be mentioned Fairbank, Warrington and Jones, Osterhaus, J. J. Thomas, Stone, Taylor and Prout.¹¹ Prout's description of the pathology is classic and will be quoted freely as follows:

Prout states that the nerve sheath in any overstretching process must give way before the nerve itself, as it supports the nerve. When the sheath is torn, as it always is in cases of birth palsy, the arterioles belonging to it and supported by it are ruptured, and a hemorrhage into the substance of the nerve and its sheath results. These facts are of the greatest importance, since they determine the ultimate extent and final character of the lesion. Were it not for the obstructive features of the repair process in the nerve sheath, we might expect a more or less complete recovery in the vast majority of cases.

Four pathologic specimens showed on study the following conditions: The usual seat of the lesion was at the junction of the fifth and sixth cervical nerves. The perineural sheath presented many old dense pigment deposits, the site of old hemorrhages. In some portions the perineural sheath was buckled inward on the nerve fibers, strangulating them and preventing their regeneration. Evidences of strangulation were present not only at these points, but also in the nerve fibers underlying these pigment deposits. There was an obliteration of the myelin sheath above and below. In the more severe cases the strands of the plexus involved came to an abrupt termination in a mass representing an old organized hemorrhage. In these cases there was a severing of the nerve fibers, which were often thrown into folds for some distance from the primary lesion. Repair of the nerve sheath takes place before regeneration of the nerve fibers, and if this has buckled inward on the nerve bundles following relief of tension, the nerve fibers are inevitably going to be strangulated and their regeneration prevented.

AUTHOR'S EXPERIMENTS²⁷

The author, by numerous dissections on infantile cadavers, has shown that traction and forcible separation of the head and shoulder puts the upper cords, the fifth and sixth cervical roots of the brachial plexus, under dangerous tension. This tension is so great that the two upper cords stand out like violin strings. Any sudden force

26. Boyer, G. F.: *Proc. Roy. Med. Soc., Neurol. Sect.*, 1912, p. 31.

27. Work done in the Laboratory of Surgical Pathology, Medical School of Harvard University, by courtesy of Dr. E. H. Nichols, director.

applied with the head bent to the side and the shoulder held would without question injure these cords. Further observation shows that forcible abduction and elevation of the arm and shoulder put the lower cords of the plexus, the eighth cervical and first thoracic on a stretch, and when much force is applied it may well lead to a tear, rupture or other injury to these segments. This condition is seen in breech cases, with arm extended. It may also follow sudden strain when the arm



Fig. 9.—Dissection of the brachial plexus in a baby, with the head and shoulder in natural relation.

is elevated, such as the so-called hostler's paralysis, caused by the sudden elevation and strain of the arm which occurs when a hostler holds a rearing horse. With the shoulder held and the head carried to one side, with the clavicle intact, considerable force was necessary to injure the plexus. The suprascapular nerve always snapped first, apparently for the reason that it had not so much freedom of play as the others. Even with considerable force the fifth and sixth cervical

nerves could not be completely torn across at Erb's point, but frayed out inside the sheath, following a partial tearing or rupture of the sheath, which always gave way first. In some cases there could be produced an evulsion from the spinal cord of the fifth and sixth cervical roots.

With the clavicle removed, the whole weight of the shoulder came practically directly on the plexus, and less force had to be exerted to cause an injury, which under these conditions was generally greater in extent, but presented the same general characteristics. It was most



Fig. 10.—Same as Figure 9, with the head and shoulder forcibly separated.

difficult to put the eighth cervical and first thoracic roots on a stretch unless the arm was abducted or hyperextended with great force.

With the clavicle intact there was apparently always enough room, even with the arm elevated and hyperextended forcibly, between the clavicle and plexus so that direct pressure from the intact clavicle on the plexus did not seem a possible cause of the paralytic condition. A fractured clavicle of course allows the weight of the shoulder to drag on the plexus, and so predisposes to greater injury from traction.

Rotation of the head combined with forcible abduction apparently does not increase the degree of tension greatly, certainly not enough to cause additional damage. In no case, even with all the force I could apply with my hands, could I rupture the joint capsule, or even separate the humeral epiphysis. Neither could I dislocate the head of the humerus. The clavicle can be broken without great force, but fracture of the other bones which go to make up the shoulder joint is practically impossible. Most birth fractures occur in the clavicle, or in the humerus, at about the junction of its upper and middle third. Stone⁹ states in the experimental work which he did that the humeral epiphysis could be easily separated, but I failed to confirm this.



Fig. 11.—Roentgenogram of the shoulder of a patient 18 years of age. Note the hooking of the acromion and subluxation of the head of the humerus, with elevation and outward rotation of the scapula.

At birth the shaft of the humerus is nearly wholly ossified, but the two extremities are cartilaginous. The scapula at birth is largely osseous, with the exception of the glenoid fossa, the coracoid and acromial process, and the posterior border and inferior angle, which are still cartilaginous. It is on account of these conditions that fractures in these regions at birth are practically nonexistent. It is not possible to produce a paralysis of the Erb type by the fracture of any bone but the clavicle.

In order to get a clear idea as to what happened to an exudate from a ruptured capsular ligament of the shoulder, in studying Lange's theory, I injected the shoulder joints of several infants with methylene blue, and then caused a rupture of the anterior portions of the joint capsule. The infants were then allowed to lie in a preserving solution on their backs for several weeks, following which time a dissection was made. In no case did the methylene blue go above the clavicle, but completely surrounded and invaded the plexus in the axilla. This would in life lead to a paralysis of the whole arm below the joint, but would in no way affect the nerves above the clavicle, and in no case would there be the typical picture of obstetric paralysis, that is, paralysis of the fifth and sixth cervical nerves. As I have stated before, why the exudate should leave the nerves alone in immediate

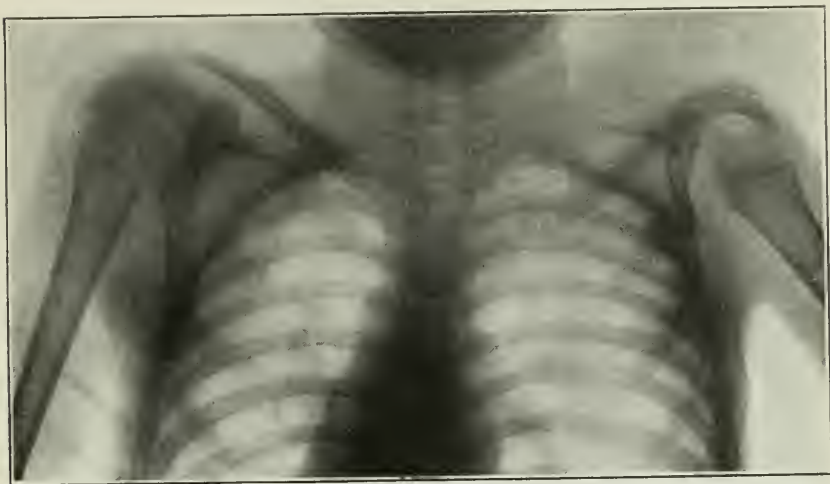


Fig. 12.—Roentgenogram of the shoulders of a boy, aged 16, showing the same characteristics as Figure 11. The normal shoulder is shown on the left.

proximity of the shoulder joint and seek out Erb's point, the junction of the fifth and sixth cervical segments, at least two or three inches above the clavicle, Lange, Thomas and others have not made quite clear. It evidently does not happen. Why also should the suprascapular nerve always be involved, which generally arises from the fifth cervical at about Erb's point? One thing impressed me, and that was the evident vulnerability of the upper cords of the plexus under any degree of traction and I was surprised that the paralysis was not of much more frequent occurrence (Figs. 9 and 10). Figure 9 shows dissection of a baby's plexus with the head and shoulders in natural relations. Figure 10 shows the head and the shoulder forcibly separated. Note the folding together of the cords of the whole plexus, especially the fifth and sixth cords.

Roentgen-Ray Findings.—One hundred and nine of the recently observed 170 cases of obstetric paralysis have had roentgenograms taken of both shoulders on one plate. These patients have varied in age from 2 days to 18 years. In only two cases had there been fracture, one of the clavicle and one of the upper third of the humerus. Both fractures had healed without incident. These cases are classified in Table 2 according to their ages at the time the roentgenogram was taken.

A study of the roentgenograms taken in these cases shows the following conditions:

In the first year there is usually nothing seen of bony deformity. There may be a slight posterior subluxation of the shoulder joint.

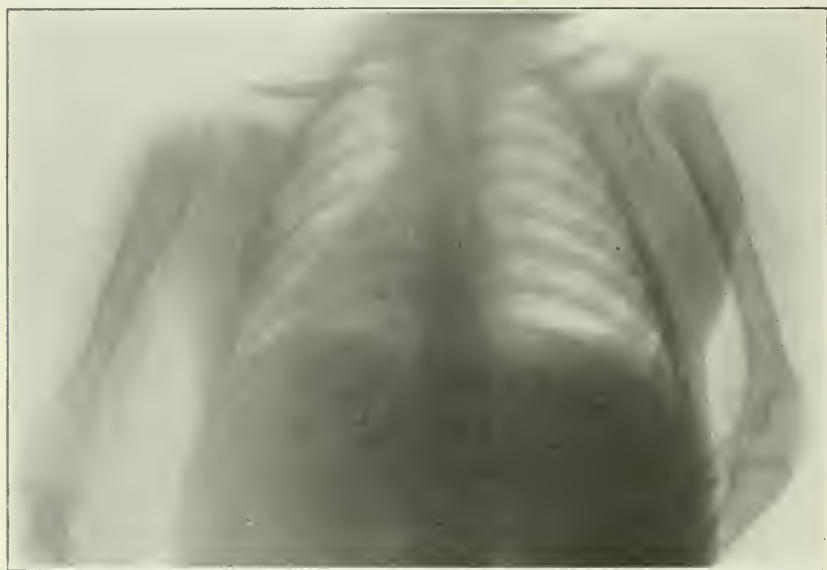


Fig. 13.—A younger patient than that shown in Figure 12. An outward displacement of the scapula is seen on the right.

but there is never any acromial deformity evident by roentgenogram or clinically. No case has been observed in which the epiphysis has been displaced so far as could be seen by comparison with the normal shoulder. The epiphysis, as well as the shaft of the humerus, is always smaller than the unaffected side, which condition is undoubtedly due to atrophy from disuse. The scapula is practically always elevated and outwardly rotated, due apparently to the pull of the intact inward rotators and the levator anguli scapulae.

As time goes on and the child gets older, one begins to see increasing evidences of bony deformity, occasionally more joint subluxation

than at first, increasing outward displacement and elevation of the scapula, and acromial deformity. The deformity of the acromion consists of a bending downward and forward or a hooking of its outer end, which apparently, having no bony resistance to meet as normally in the head of the humerus, projects downward in front of the subluxated and inwardly rotated head. This hooking seems to vary directly with the degree of posterior subluxation and inward rotation of the humerus and tends to increase as the child gets older, provided

TABLE 2.—CONDITION SHOWN BY ROENTGENOGRAM IN 109 CASES

Ages, Years	Subluxation of Joint	Acromial Deformity	Elevation and Displacement Outward of Scapula	Joint Apparently Normal
*	11	.	16	15
1	6	3	7	5
2	5	1	5	5
3	4	3	5	4
4	4	4	6	4
5	6	6	6	
6	3	4	5	2
7	5	3	6	
8	2	1	3	
9	4	4	4	
10	3	3	3	
11	2	2	2	1
12	1	1	1	
13	2	1	2	
14	3	2	3	
15	1	1	1	
16	1	1	1	
17				
18	1	1	1	

* Age from 1 day to 2 years.

subluxation is present. No case has been observed in which there has been a total subluxation or dislocation of the shoulder joint backward. The clavicle usually is shorter and its curves are more acute than its normal fellow (Figs. 11, 12 and 13).

Clinical Findings.—When the child is first seen, if within a few days or weeks after birth, the following picture is classic. The arm lies limp at the side, extended and inwardly rotated, with complete inability to abduct, elevate, outwardly rotate or supinate. The muscles

paralyzed in the typical upper arm type are as follows: Deltoid, supraspinatus, infraspinatus, teres minor, biceps, supinator longus, and occasionally the serratus magnus, coracobrachialis and supinator brevis. The arm cannot be actively flexed at the elbow, but as a rule the lower arm is not affected so far as flexion and extension of the wrist and flexion and extension of the fingers go (Figs. 14 and 15).

The greater part of the motor nerve supply to these paralyzed muscles depends on one root alone, although fibers from more than one root can be traced to individual muscles of the arm. The root distribution of the nerves of the brachial plexus is as follows (Quain²⁸):

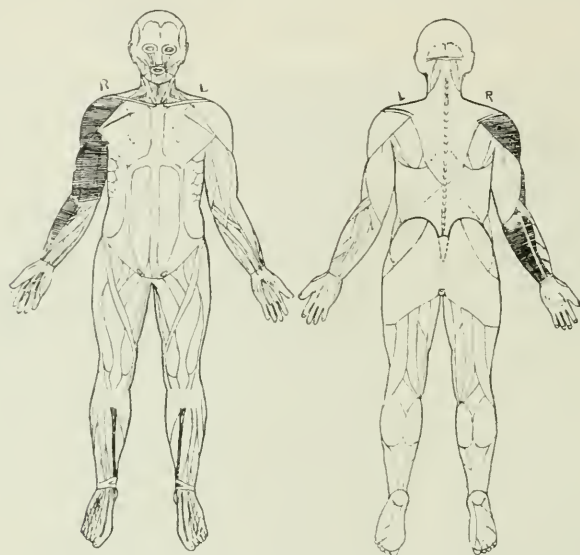


Fig. 14.—Typical upper arm type of obstetric paralysis in a girl of 10 weeks; the muscles shown in white are normal, those in dark shading are paralyzed.

The fifth cervical supplies the levator scapulae, rhomboidei, serratus magnus, supraspinatus, infraspinatus, teres minor, subscapularis, deltoideus, biceps brachii, brachialis anticus (?), pectoralis major (?), teres major.

The sixth cervical supplies the serratus magnus (?), supraspinatus (?), infraspinatus (?), teres minor, subscapularis, teres major, deltoideus, pectoralis major, biceps brachii, brachialis anticus, pronator teres, flexor carpi radialis, supinator longus and brevis, extensor carpi radialis, abductor opponens and flexor brevis pollicis.

The seventh cervical supplies the serratus magnus, pectoralis major and minor, latissimus dorsi (?) teres major, coracobrachialis, triceps

28. Quain: Anatomy, iii, Part 2, p. 354.

brachii anconeus, flexor sublimis digitorum (?), flexor profundus digitorum (?) flexor longus pollicis (?) pronator quadratus, extensor radialis, extensores digitorum, extensor carpi ulnaris (?) abductor opponens (?) and flexor carpi pollicis (?).

From the eighth cervical are supplied the pectoralis major and minor, latissimus dorsi, triceps, anconeus, flexores digitorum, flexor carpi ulnaris, pronator quadratus, adductor pollicis, interossei, abductor flexi brevis and opponens, and abductor minimi digiti.

From the first dorsal are supplied the pectoralis major and minor, flexores digitorum, flexor carpi ulnaris, pronator quadratus.

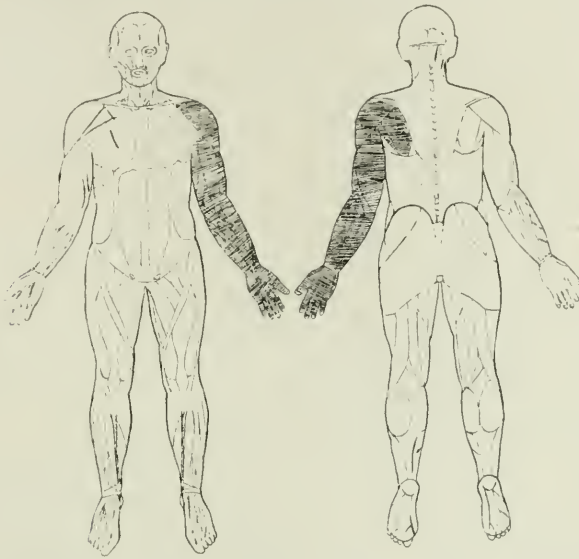


Fig. 15.—Typical lower or whole arm type of obstetric paralysis in a girl of 3 months; the muscles shown in white are normal, those in dark shading are paralyzed.

Tracing back the nerves to their origin, we find the following facts:

From the outer cord: The external anterothoracic follows back to the sixth, seventh and fifth (?) cervical; the nerve to the coracobrachialis to the seventh cervical; the musculocutaneous to the fifth and sixth cervical; the outer head of the medianus to the sixth and seventh cervical.

From the posterior cord: The upper subscapular is traceable to the fifth and sixth cervical; the lower subscapular to the fifth (?) and sixth cervical; the circumflexus to the fifth and sixth cervical, and the musculospiral to the sixth, seventh and eighth cervical (Fig. 5).

It should be noted that a number of these muscles have more than

one source of supply. Expressed in terms of motion the condition is as follows:

Flexion of the elbow is carried out by the fifth cervical; extension of the elbow by the seventh cervical; pronation of the hand by the sixth cervical; supination of the hand by the fifth cervical; flexion of the wrist by the eighth cervical, and extension of the wrist by the seventh cervical.

In the upper arm type then, the nerves involved are the suprascapular, from the fifth cervical root and outer cord of plexus, going to the supraspinatus and infraspinatus muscles. The musculocutaneous from the fifth and sixth cervical roots and outer cord of the plexus, going to the coracobrachialis, biceps and brachialis anticus. The circumflex from the fifth and sixth, and possibly the seventh and eighth and posterior cord of the plexus, going to the deltoideus and teres minor. The musculospiralis from the fifth, sixth and seventh, and also possibly some fibers from the eighth cervical and posterior cord of the plexus, going to the supinator longus and brevis, brachialis anticus, triceps, anconeus and extensors of hand.

The fact that in the upper arm type practically the only muscles supplied by the musculospiralis which are paralyzed below the elbow are the supinators goes to show that either the injury is not extensive or that the nerve root supply is well divided. No two diagrams of the brachial plexus among all that I studied were alike. The cut of the one shown is the most satisfactory, and, as far as I could tell, the most usual type of formation of the plexus (Fig. 5).

In order to get this definite and constant paralytic muscle grouping, the injury would have to be located at about the junction of the fifth and sixth cervical nerve roots, just above the point of origin of the suprascapular nerve. This junction point is called Erb's point, from his classic description of the type of paralysis seen following injury at that point.

The inability to raise or abduct the arm at the shoulder is due to the paralysis of the deltoideus and supraspinatus. Outward rotation cannot be accomplished because of the paralysis of the infraspinatus and teres minor, and the arm cannot be internally rotated owing to the internal rotators, namely, the teres major, subscapularis and latissimus dorsi, being already fully contracted, due to lack of opposition.

The arm cannot be flexed at the elbow, owing to the paralysis or weakness of the biceps, brachialis anticus, coracobrachialis and supinator longus; and supination cannot be carried out owing partially to the inward rotation in which the arm is held and the weakness or paralysis of the biceps and supinator longus and brevis.

In regard to sensation, it may be stated that it has been impossible

TABLE 3.—ANALYSIS OF 394 CASES OF OBSTETRIC PARALYSIS, SHOWING CONDITION AT DIFFERENT AGES, AGE WHEN SIGNS OF RECOVERY WERE NOTED, AND IN THE OLDER PATIENTS THE CONDITION ON ENTRANCE TO CLINIC

Age	Complete Paralysis		Partial Recovery		Total Recovery		Elevates to Shoulder or Above		Wrist Drop	Paralysis of Hand, Partial or Complete
	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower		
2 weeks.....	11
3 weeks.....	5	..	4	1
5 weeks.....	7	..	7
6 weeks.....	3	1	2	1	1	1
7 weeks.....	7	..	7	2	1
2 months.....	8	2	14	..	1	..	6
10 weeks.....	1	..	7	4
3 months.....	3	3	27	1	10	1	2	..
4 months.....	12	1	6	1	1	1
5 months.....	..	1	9	7
6 months.....	15	1	15	1	1	..
7 months.....	10	9
8 months.....	..	3	11	3	9	1	3	3
9 months.....	12	11
10 months.....	3	2
1 year.....	48	7	1	..	47	5	6	4
2 years.....	27	5	26	3	5	3
3 years.....	..	1	16	2	15	1	3	3
4 years.....	19	2	2	..	19	2	2	1
5 years.....	7	2	7	2	3	1
6 years.....	12	2	1	..	12	1	2	2
7 years.....	..	1	6	2	6	2	3	2
8 years.....	8	..	1	..	7
9 years.....	4	4
10 years.....	3	..	1	..	2
11 years.....	6	1	7	..	1	..
12 years.....	2	2

in the early cases to determine any changes from the normal, on account of the age of the patient. Likewise, electrical reactions have not been carried out, for this examination would mean anesthesia, which did not seem justifiable in such young children, when one already had all necessary data.

During the first week, in the early cases, the child may cry if the arm is handled or moved, especially in abduction, but this soon disappears. In one or two cases there has been some swelling and tenderness noted by palpation over the plexus above the clavicle. This condition, however, apparently had no connection with the degree of paralysis present. The hand grasp is usually good and the child flexes and extends the wrist and fingers well. The later developments in the upper arm cases, as the child grows and gets older, with or without exercises and massage, are as follows: The persistence of the inward rotation and adduction deformity, the so-called policeman's tip position; the inability in most cases to fully or freely supinate; the inability to get the hand to the mouth without raising the elbow, due to inability outwardly to rotate; the inability to put the hand to the head or behind the back.

In the lower arm type all these conditions hold, besides the additional ones due to the paralytic conditions of the lower arm and hand, resulting generally in a useless dangle arm.

Atrophy of the muscles in these cases of obstetric paralysis is never very marked, except in some cases of the lower arm type. One never sees the extreme atrophy so noticeable in cases of infantile paralysis. This lack of marked atrophy is undoubtedly due to the fact that the nerve impulses are rarely fully blocked and that the muscles practically never, except in rare cases, wholly lose their entire enervation. Some normal nerve impulses pass through the scar tissue at the site of the lesions, owing to incomplete destruction or injury of the nerve, and so keep the muscle tone up to a certain point. There is always a definite shortening of the arm, however, in all cases, due probably as much to nerve injury as lack of use.

Referring to Table 3, which shows the detail of the cases reported, we may note that there are 400 of the upper arm type of paralysis. These in the main showed the conditions mentioned above.

SUBSEQUENT DEVELOPMENTS

Whole Arm Type, Lower Arm Type.—There were seen sixty-four cases of this type in this present series. In this classification those cases which showed any nerve involvement beyond that usually shown by an injury of the fifth and sixth cervical roots were placed. These cases represented those injuries mainly to the whole of the plexus, or at least the seventh and eighth cervical and the first dorsal roots.

Pupillary inequality and narrowing of the palpebral fissure were not unusual with this type. Wrist-drop was the usual condition, associated with the usual inability to supinate and the additional inability to extend the lower arm. Paralysis of the flexors and extensors of the wrist and fingers were common, associated with paralysis and atrophy of the intrinsic muscles of the hand. Often the proximal phalanges are hyperextended, and the distal ones flexed, due to the paralysis of the interossei or lumbricalis manus muscles. There is, of course, no power to grip and the fingers cannot be moved. There is usually ulnar displacement or adduction of the hand. These cases, almost without exception, represent severe tearing injuries to the roots of the

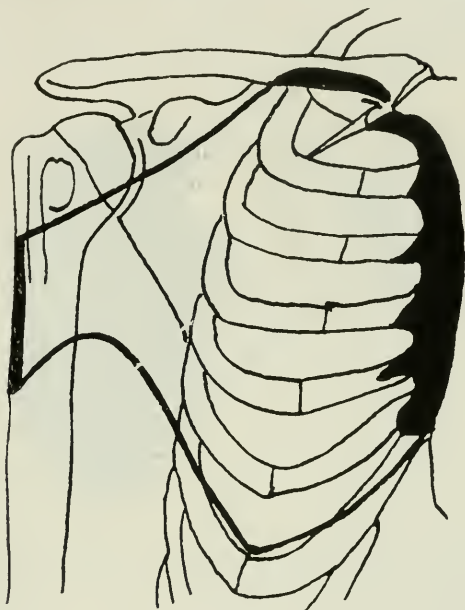


Fig. 16.—Pectoralis major of right side; outline and attachment areas (Gerrish).

plexus, and although some of the muscles may recover in part, particularly the upper arm and shoulder groups, the lower arm ones practically never recover, even after attempted operative repair of the plexus. It is in these cases that sensation is more apt to be impaired than in the usual upper arm type. A not uncommon type seen is one showing simply a wrist-drop, associated with the usual picture of upper arm paralysis and evidence of injury to the fifth, sixth and seventh cervical roots. These cases, as far as results go, should be classed with the simple upper arm type. Few cases have been recorded in which the two lower roots alone have been involved. These have been reported fully by J. J. Thomas.⁷

The complications may be divided into two classes, early and late. The early complications are those accompanying the paralysis and present at birth. The following may be mentioned:

Facial paralysis is usually mild and on the same side as the paralyzed arm and is probably from forceps pressure on the facial nerve.

Fracture of clavicle is not rare.

Separation of epiphysis of the head of the humerus may occur, but no case is noted in this series; it might be grouped under the pseudoparalysis of D'Astros and Danchez.

Dislocation of the humerus sometimes is present, usually infra-spinatus. This complication is not noted in this series, but is recorded by other observers.

Fracture of the upper third of the humerus may also occur.

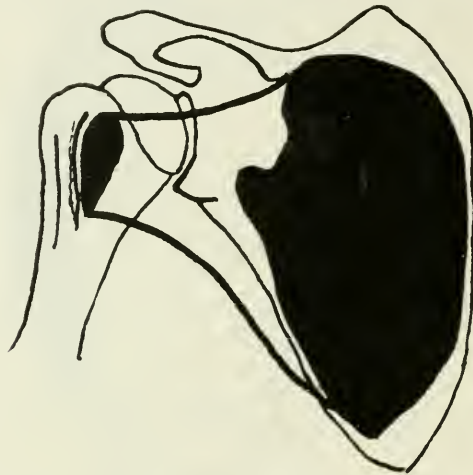


Fig. 17.—Subscapularis of right side; outline and attachment areas (Gerrish).

As late complications the following may be mentioned:

Posterior subluxation of the humerus is common and due to contraction of unparalyzed pectoralis major, subscapularis and teres major (Figs. 16 and 17).

Hooking of the acromion may occur, as has been already noted above.

Anterior subluxation of the humerus, due to the pull of the contracted pectoralis major and the stretching of the subscapularis, is not uncommon.

Contraction of the biceps and the brachialis anticus, leading to some degree of permanent flexion deformity at the elbow and occasionally dislocation of the head of the radius, may occur.

An analysis of Table 4 may be of interest. In the first place, there is no reason to expect any difference in regard to the sex, unless one

is ready to accept Simpson's theory that girls' heads, being smaller, and so not dilating the canal sufficiently, would subject them to a more difficult labor, and so to a greater percentage of occurrence of injury to the brachial plexus. These figures, representing by far the largest number of cases so far reported, and outnumbering all others reported by all observers, do not confirm his theory.

The right arm was affected 272 times and the left 186, about 68 per cent. in favor of the right arm. This bears out Sharpe's figures in his series of fifty-six operative cases. Nine babies had both arms affected.

The types of paralysis differed, the most usual one being the so-called upper arm type, 400 being recorded, as against the so-called lower or whole arm type, in which, besides the fifth and sixth cervical cords being injured, the seventh and eighth cervical and first dorsal

TABLE 4.—CONDITIONS EXISTING AT THE TIME OF BIRTH

Boys	235
Girls	236
Total	471
Right arm affected.....	272
Left arm affected.....	186
Both arms affected, upper arm type.....	2
Both arms affected, lower or whole arm type.....	1
Both arms affected, type not noted.....	6
Upper arm type.....	400
Lower or whole arm type.....	64
Difficult labor	418
Ether used	363
Forceps used	317
Normal labor	32
Asphyxiation of child.....	102
Head presentation (including face).....	219
Breech presentation (including foot and version).....	66
Position not known.....	186
Fractured clavicle	14
Arm broken	3
Cord around neck and arm.....	2
Cord around neck.....	2
Pupils unequal	16

were injured. Of the latter type sixty-four cases were recorded. In nine cases with both arms affected the lower or whole arm type of paralysis showed generally.

It has been conceded by practically all authors that a difficult labor was a predisposing factor in the causation of paralysis. In this series 418 cases were definitely recorded as long, laborious and difficult; 363 at least had ether and 317 had forceps used; thirty-two were apparently normal labors and 102 were recorded in which the child was asphyxiated.

All the conditions noted above imply the application of force combined with great muscular relaxation of the child, conditions peculiarly favorable for the production of such an injury. A moderately large number, it is recorded, had the head delivered naturally, but the shoulders stuck, and at that time force was applied.

In regard to the presentations, 219 at least were vertex or face presentations and sixty-six were breech. The latter classification includes versions and footlings. In 186 the position was not recorded, but a large majority of these were probably vertex. These figures do not bear out either Tubby or Sherren (quoted under Fairbank¹⁸), who state that the paralysis occurs equally in head or breech presentations. Fairbank's own figures refute this also, for he reported in forty cases thirty-two vertex and seven breech. These figures cover 285 cases of the author's in which the presentation was definitely known.

The other conditions occurring at birth may be noted in Table 4. and I want to add a word about only one of them, namely, that of unequal pupils. This condition is probably overlooked in some cases, and is a most important symptom, in that it means that through injury to the cervical sympathetic there may be definite injury to the plexus either of the lower cords, the eighth cervical or first dorsal, which have communicating bands with the cervical sympathetic, or injury in the spinal cord itself to the fibers of the sympathetic system. The prognosis in these cases is usually not so good as in those which do not show this sign.

TREATMENT

As to treatment, these cases at once resolve themselves into two divisions, namely, those to be treated with massage and exercises, principally those of the upper arm type; and those to be treated by operation on the plexus, usually those of the lower arm type. Unless the early treatment has been adequate, the upper arm type will also come to operation, not for plexus repair, but to correct contraction deformities. This operation, which I have devised, will be spoken of later.

At first, in order to prevent contraction of unparalyzed muscles, it seems best to put the arm at rest in such a position that the muscles cannot become contracted. This may be done by holding the arm in a plaster cast, or by the use of a light wire splint, in an abducted, elevated and outwardly rotated position, with the hand supinated. This position can be maintained between massage and gymnastic treatments, and insures a better subsequent position of the arm. It also takes the drag off the paralyzed muscles, allowing them to regain their strength more quickly, and prevents subsequent shoulder joint deformity, such as subluxation and acromial hooking and overgrowth.

Massage and exercises are of the greatest importance and should be done daily if possible. It is most unwise to allow a child to become obsessed with the fact that it has an arm which cannot be used. Exercises which have been described in detail by J. J. Thomas²⁹ are

29. Thomas, J. J.: *Obstetrical Paralysis with Especial Reference to Treatment*, Boston Med. and Surg. Jour., April 2, 1914, clxx, No. 14.

most satisfactory, and have been developed during the past twenty years in the neurologic department of the Children's Hospital. The treatment should be continued for several years at least, and if contractures develop in the subscapularis and pectoralis major, they must be divided before any further range of action in the arm is to be hoped for.

In regard to the operation on the plexus in the usual upper arm type of case, it might be said that in the experience of this clinic it has not been found necessary. In the lower arm type of cases the situation is quite different, but it cannot be too strongly emphasized that no operation on the plexus will be of any great use in restoring functional activity to the arm, unless contracted and restricting muscles are divided, and careful after-treatment persisted in for a long period.

In regard to the operative treatment on the plexus in the lower arm type of case, it may be stated that it has been done a number of times without any benefit. The plexus in all cases was found to be so badly torn and so bound down and invaded by scar tissue that any kind of repair was impossible. In spite of the work done by A. S. Taylor,¹¹ Stone,⁹ Fairbank¹⁸ and others, there has been no case as yet which has shown an anatomic or physiologic cure, or even a marked improvement. This may be due to the fact that in the first place the plexus was impossible to repair, and secondly, granted that the plexus repair was in part possible, the muscular contractions and joint deformities were not recognized and properly treated, without which the attempt to obtain plexus repair would be a waste of time and effort.

The following operation was devised, following suggestions made by Fairbank.¹⁸ It differs from Fairbank's operation in that the shoulder joint is not opened. Opening this joint leads to adhesions of the capsule, which are troublesome and fatal to the best functional results. In addition, I have found that complete division of the pectoralis major is always advisable, in that it is practically always tightly contracted, and so holds the arm adducted and prevents abduction and outward rotation. The subscapularis tendon can usually be easily found with the arm abducted and outwardly rotated after the division of the pectoralis major, and can be divided without opening the joint capsule.

OPERATION

An incision is made situated on the anterior aspect of the arm and extending from the clavico-acromial joint to a point below the lower edge of the pectoralis major tendon. The incision is carried down between the deltoid and clavicular portions of the pectoralis major, tying or retracting the cephalic vein. The tendon of the pectoralis major is isolated and divided on a director. Turning the cut pectoralis

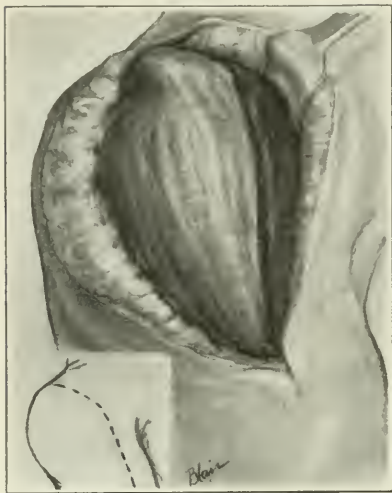


Figure 18



Figure 19

Fig. 18.—The skin incision and the incision between the deltoid and pectoralis major.

Fig. 19.—The pectoralis major cut and the deltoid and the pectoralis major retracted; the long head of the biceps is in the floor of the wound.

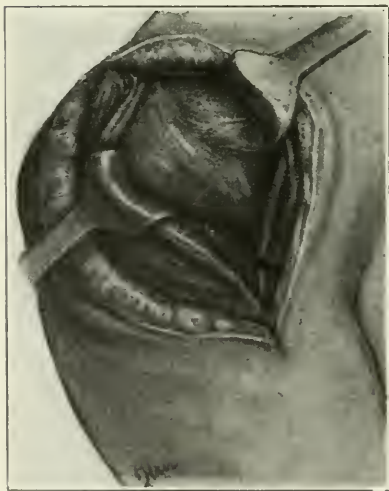


Figure 20

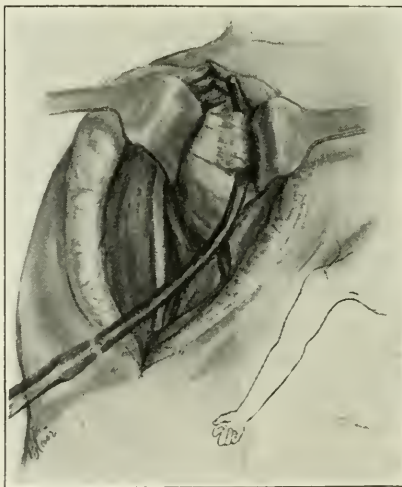


Figure 21

Fig. 20.—The joint capsule with the insertion of the subscapular tendon on inner aspect.

Fig. 21.—A sound is passed under the tendon of the scapularis, the arm being abducted and rotated out to its limit.

major back and retracting the deltoideus gives a good view of the long head of the biceps and the joint capsule, as well as the short head of the biceps and coracobrachialis. The arm is now abducted and outwardly rotated, bringing into view the transverse fibers of the tendon of the subscapularis at its point of insertion into the joint capsule at its inner and anterior aspect. This tendon is isolated and a sound or other blunt instrument is passed under it, and it is then divided. In this way not only is the pectoral divided, which, when contracted, prevents abduction, but also the subscapularis is divided,



Fig. 22.—E. L., October, 1915. Before operation on right arm.

which, when contracted, prevents outward rotation. It is better to divide the subscapularis by this method, rather than to open the joint capsule, after Fairbank's method, for it does not lead to subsequent adhesion of the capsule to the joint cartilage and consequent loss of motion.

After these two structures have been cut, outward rotation and abduction will usually be found to be perfectly free. In case either is at all restricted, the coracobrachialis or the short head of the biceps may be found to be tight, and the partial division of these structures

will always lead to full freedom in outward rotation and abduction. If the head of the humerus is blocked by the hooking downward of the acromion in front of it, so that the posterior subluxation cannot be fully reduced, an osteotomy can be easily done on the acromion, through the upper end of the original incision.

If there is an anterior subluxation of the joint, which occurs rarely, the pectoralis major is the only muscle which needs to be divided. A division of the subscapularis would only tend to increase a deformity already present. The pectoralis major and deltoideus are then joined with interrupted catgut sutures, and the skin closed by a continuous catgut suture. The arm is then put into a plaster cast extending from the crest of the ilium to the tips of the fingers, the arm being abducted, elevated, outwardly rotated and the hand supinated. This cast should be worn only about two weeks, at the end of which time baking,



Fig. 23.—E. L., April 12, 1916. Three months after operation on right arm.

massage and exercises should be started and continued daily for several months. After two or three weeks a wire splint may be substituted for the cast, in that it is lighter and more comfortable (Figs. 18, 19, 20 and 21).

RESULTS OF OPERATION

Twelve patients so far have been operated on. The first few operations were done by Fairbank's method and the patients were kept in plaster for the length of time advised by him, namely, three months. It is too long. Although they were improved, it has required persistent effort and considerable difficulty to restore motion in the shoulder joint, besides muscle strength, and the results were not commensurate with the time and effort expended.

Recently, since I have been doing the operation described above, combined with early treatment, that is, by giving massage, manipulation



Fig. 24.—R. B., Nov. 17, 1915. Right arm before operation.



Fig. 25.—R. B., April 26, 1916. Five months after operation on the right arm.

and exercises, at the end of two weeks the results have been much better. This is what might have been expected. Once the contractions are divided, long fixation is obviously unnecessary (Figs. 22, 23, 24 and 25).

PROGNOSIS

The prognosis in all upper arm type of cases is good, provided the case is watched from the start, and treatment properly carried out. The patients are practically all able to raise the arm to the shoulder level and can use the hand and lower arm well, except for varying degrees of supination. Abduction and outward rotation are rarely regained without division of the contracted muscles, provided they have been allowed to contract.

In the lower arm type the outlook is not so good, although many of the patients regain use of the upper arm in spite of the persistent paralysis of the lower arm and hand. These cases should all be explored for repair of the plexus as far as possible, but even then very little hope can or should be held out to the parents. The general principle of treatment, however, should be carried out over a long period of time. Much can be done along orthopedic lines for these patients, and they should not be generally neglected as they have been in the past, with the statement that nothing can be done, or that they will get well of themselves (Table 3).

CONCLUSION

Obstetric paralysis is due to a stretching or tearing of the cervical roots of the plexus brachialis. It occurs in boys as frequently as in girls. It occurs more often on the right than on the left side.

The upper arm type is much more frequent than the lower arm type. It affects both arms very infrequently.

It is practically always associated with a difficult labor, in which ether and forceps have been used and force has been applied. Not uncommonly is the baby asphyxiated.

Head presentations show the larger percentage of occurrences of both types of cases.

It may rarely be associated with fracture of the clavicle, but is not the result of a fractured humerus or a dislocated shoulder joint.

The prognosis for a useful arm is good in the upper arm type and bad in the lower arm type.

A STUDY OF THE TOPOGRAPHY OF THE PULMONARY FISSURES AND LOBES IN INFANTS

WITH SPECIAL REFERENCE TO THORACENTESIS *

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In the course of a general study of the anatomy of the infant's chest it seemed to us desirable to attempt to determine accurately the relation of the fissures of the lung to the bony framework of the thorax. We felt that carefully obtained data would be valuable not only for comparison with similar relations as they exist in the adult, but also as a stimulus toward greater accuracy in the clinical diagnosis of pleuropulmonary disease.

A careful search of the standard textbooks and of the periodical literature which has appeared since 1905 shows nothing in reference to the course of the fissures in infants. Symington¹ states that the only gross difference between the position of the lungs in children and in adults lies in the fact that in the former the anterior margins of the lungs are not as closely approximated as in the adult, in other words, that the right and left lungs at times do not meet or overlap under the manubrium sterni. He makes no mention of any difference in the course or relations of the fissures. On the other hand, there are numerous references pertaining to adults. Many of these doubtless are mere copied repetitions, but the conflicting descriptions point to the conclusion that the course of the interlobar fissures is fixed only within comparatively wide limits.

The right lung, it will be remembered, normally possesses two fissures. One of these, the oblique, starts above and behind and runs downward, outward and then forward; the second, the horizontal fissure, begins at a variable point above the middle of the oblique fissure and passes almost horizontally in toward the sternum.

The left lung normally possesses but a single fissure, the oblique, which corresponds to the like structure on the right side.

Various anomalous fissures exist quite frequently, the most common, according to Shaffner,² being found on the lower surface of the

* From the Laboratory of Anatomy of the University of Pennsylvania.

1. Symington, J.: *The Anatomy of the Child*, E. & S. Livingstone, Edinburgh, 1887, p. 64.

2. Shaffner, quoted by Piersol, George A.: *Human Anatomy*, J. B. Lippincott Co., Philadelphia, 1907, p. 1846.

lower lobe. This is sometimes merely a shallow indentation, but at others is a deep fissure sharply delimiting the inner portion of the lower lobe.

In addition to anomalous fissures, there are also found at times variations in the normal fissures. Of the latter the horizontal is the one most frequently found to be atypical and at times it may be absent. Conversely, in the left lung, a transverse fissure occasionally is found dividing it into three lobes.

That the course of the oblique fissures in adults is far from constant may be inferred from the descriptions found in the literature.

Right Lung: It begins at the second dorsal vertebra (Morris,³ Gray,⁴ Deaver⁵), the second or third (Spalteholtz⁶), the third (Fraenkel⁷), the third or fourth (Corning⁸), the fourth (Bickham,⁹ McClellan,¹⁰ Davis,¹¹ Chauffard¹²), the fourth interspace or the fifth rib (Rochard¹³), the fifth rib or the fourth or fifth interspace (Piersol¹⁴). It terminates at the fifth intercostal space or the sixth rib (Rochard,¹³ Gray,⁴ Davis,¹¹ Morris,³ Deaver,⁵ Piersol¹⁴), the seventh rib (Bickham,⁹ McClellan,¹⁰ Fraenkel⁷), the eighth rib (Chauffard¹²).

Left Lung: It begins at the second dorsal vertebra (Gray,⁴ Morris,³ Deaver⁵), the second or third dorsal vertebra (Spalteholtz⁶), the third rib (Bickham,⁹ Fraenkel,⁷ McClellan¹⁰), the third or fourth rib (Corning,⁸ Davis¹¹), the fourth interspace (Chauffard¹²), the third to the fifth rib (Piersol¹⁴). It terminates at the sixth rib according to most of these authorities, except Chauffard,¹² who finds it at the seventh interspace.

Authors' Technic.—Our own observations are based on dissections

3. Morris, Sir Henry: *Human Anatomy*, edited by J. P. McMurrich, P. Blakiston's Sons & Co., Philadelphia, 1907, Part 5, p. 1295.

4. Gray, Henry: *Human Anatomy*, edited by Robert Howden, Lea & Febiger, Philadelphia and New York, 1913, p. 1299.

5. Deaver, John B.: *Surgical Anatomy*, P. Blakiston's Son & Co., Philadelphia, 1903, iii, 409.

6. Spalteholtz, quoted by Dietlen, H.: *Ergebn. d. inn. Med. u. Kinderh.*, 1913, xii, 197.

7. Fraenkel, A.: *Therap. d. Gegenw.*, 1910, li, 337.

8. Corning, quoted by Dietlen, H.: *Ergebn. d. inn. Med. u. Kinderh.*, 1913, xii, 197.

9. Bickham, Warren S.: *Operative Surgery*, W. B. Saunders Co., Philadelphia, 1908, p. 772.

10. McClellan, George: *Regional Anatomy*, J. B. Lippincott Co., Philadelphia, 1892, i, 267.

11. Davis, G. G.: *Applied Anatomy*, J. B. Lippincott Co., Philadelphia, 1913, p. 198.

12. Chauffard: *Rev. gén. de clin. et de therap.*, 1914, xxviii, 420.

13. Rochard, quoted by Gary, M. P.: *Arch. de méd. et pharm. mil.*, 1910, lvi, 104.

14. Piersol, George A.: *Human Anatomy*, J. B. Lippincott Co., Philadelphia, 1907, p. 1859.

of the formaldehyd-hardened bodies of fourteen infants, varying in age from 6 weeks to 15 months. Of these, six were under 4 months of age and six were 4 months or older; in two the exact age was unknown, but it approximated 3 to 6 months. In order to expose the fissures in exact relation to the ribs, all of the soft tissues covering the ribs, sternum and spine, as well as the intercostal muscles and the parietal layer of the pleura, were carefully removed. Enough of the muscles of the shoulder girdle were left to insure stability of the clavicles, scapula and upper ribs. To allow of access to the interior of the chest the sternum was freed, the attachments of the costal cartilages

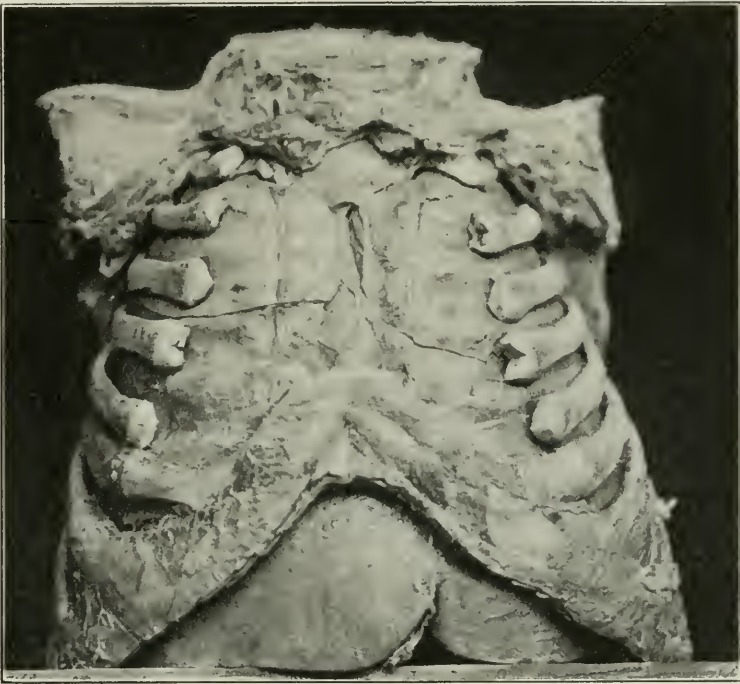


Fig. 1.—Photograph of a thorax showing the method of preparing the specimens for studying the relations of the pulmonary lobes and fissures in situ.

being noticed in order to insure accurate replacement. The spine was allowed to remain untouched as a permanent support. As the bodies had been injected with formaldehyd, the manipulations essential to study in no wise disturbed the relationship of the structure as it had existed at the time of death. The photograph (Fig. 1) shows to a certain extent the result of one of the dissections, but it is impossible to depict in this manner the entire course of the fissures in relation to the ribs. By gentle separation of the ribs, however, this could accurately be determined in every case.

Unfortunately, the removal from our specimens of the soft tissues of the chest destroyed all the ordinary clinical landmarks of the axillary region. This is to be regretted, since the point of origin of the horizontal fissure from the oblique is a matter of considerable practical interest, mainly because it is the most obvious point of attack in dealing with a collection of pus between the upper and middle lobes.

An attempt was made to compensate for this loss of landmarks by marking the ribs with an indelible pencil or by nicking them with a knife before removing the pectoral and latissimus dorsi muscles. Neither of these methods was successful, as the pencil marks became smeared in the course of the subsequent dissection and the incisions into the ribs rendered them so fragile that the attempt was abandoned. In place of this we established the midpoint of the axilla by bisecting a horizontal line drawn from midsternum to the spinous process at a point just below the angle of the scapula. This we have called the midthoracic line.

In twenty-eight children in the wards of the Children's Hospital, varying in age from 15 days to 5 years, we compared the relation between this midthoracic line and the usual landmarks of the axilla, namely, the midaxillary and postaxillary lines. The latter landmarks were first located and carefully marked, and then the measurements for the midthoracic line were taken and compared with these markings. It was found that the midthoracic line invariably lay posterior to the midaxillary line, a distance varying from 0.5 to 2.5 cm. (average of all cases, 1.27 cm.), while the postaxillary line lay posterior to the midthoracic line in every case but one, the distance varying from 0.5 to 1.5 cm. (average of all cases, 0.92 cm.). In the one exception, a child of 4 years, the midthoracic line lay 0.4 cm. posterior to the midaxillary line and exactly in the postaxillary line.

In general, we may say, therefore, that the midthoracic line lies approximately midway between the midaxillary and postaxillary lines. As the determination of the clinical landmarks by the eye is not so accurate or so reliable as the actual measurement by the tape, the latter procedure possesses distinct advantages.

Authors' Findings.—Our studies have shown us that the course of the pulmonary fissures in the infant may be described as follows:

Right Lung, Oblique Fissure: The origin is from the third to the fifth rib at the spine. In ten out of fourteen the point of origin was at the fourth rib or fourth interspace, in three at the third rib or third interspace and in one at the fifth rib, the average of fourteen cases being the fourth rib.

The course is downward and forward, crossing the midthoracic line between the third rib and the sixth interspace. Of the fourteen cases, one crossed at the third rib, two at the fourth rib, five at the

fifth rib or fifth interspace and six at the sixth rib or sixth interspace, the average of fourteen cases being the fifth rib.

The termination is from the sixth to the seventh rib just posterior to the costochondral junction. Four were at the line of the costochondral junction and ten were from 1 to 3 cm. posterior to it. Of the fourteen cases, six terminated at the sixth rib, two at the sixth interspace and six at the seventh rib, the average of fourteen cases being the sixth interspace.

Right Lung, Transverse Fissure: The origin is from the third interspace to the sixth rib in the line of the oblique fissure. Of the fourteen cases, one was at the third interspace, seven were at the fourth rib or fourth interspace, five at the fifth rib or fifth interspace and one at the sixth rib, the average of fourteen cases being the fourth interspace.

The course is almost horizontal, either beneath the fourth rib or the interspace above or below it.

The termination is at the edge of the sternum from the third rib to the fourth interspace. Of the fourteen cases, six were at the third rib or third interspace, seven were at the fourth rib or fourth interspace and one was anomalous, terminating in the second interspace 3 cm. to the right of the sternal border, the average of thirteen cases being the upper border of the fourth rib.

Left Lung, Oblique Fissure: (In one case this fissure began at the fifth rib, passed downward more vertically than usual, crossing the midthoracic line at the eighth rib. Thence it continued forward beneath the eighth rib to its costochondral junction, an anomalous type. This is excluded from the summaries of this side, leaving but thirteen.)

The origin is from the second to the fifth rib. Of the thirteen cases, four were at the second rib or second interspace, two at the third rib or third interspace, seven at the fourth rib, the average of thirteen cases being the third interspace.

The course is downward and forward, crossing the midthoracic line behind the third to the sixth rib. Of the thirteen cases, one was at the third rib, four were at the fourth rib or fourth interspace, four at the fifth rib and four at the sixth rib. Average of thirteen cases, fifth rib.

The termination is from the sixth to the seventh rib at or posterior to the costochondral junction. Seven were at the line of the costochondral junction and the remainder about 1 cm. posterior to it. Of the thirteen cases, seven were at the sixth rib and six at the seventh rib, the average of thirteen cases being the sixth interspace.

To sum up, we find that the oblique fissure of the right lung in infants begins at the fourth rib (from the third to the fifth as extremes), crosses the midthoracic line between the fourth and sixth

ribs and terminates between the sixth and seventh ribs, at or just posterior to the costochondral junction. In adults, according to the literature, the origin seems to be somewhat higher, although the tip of the dorsal vertebra, which is used as a landmark by some authors, almost corresponds to the rib below it, the second dorsal vertebra is equivalent to the third rib, etc. The point of termination seems to be the same in both infants and adults.

The oblique fissure of the left lung in infants begins at the third interspace (from the second to the fifth ribs as extremes), crosses the midthoracic line between the fourth and sixth ribs (as on the right side) and terminates between the sixth and seventh ribs, at or just posterior to the costochondral junction. In adults the origin and termination are described as being about the same as our findings in the infant.

The transverse fissure in infants begins at the line of the oblique fissure between the fourth and fifth ribs (from the third to the sixth rib as extremes) just in the midthoracic line or more often slightly posterior to it, and passes horizontally inward to terminate at the junction of the fourth rib or interspace and the sternum. In adults the exact beginning of the transverse fissure usually is not clearly described by the authorities consulted, but apparently it corresponds very closely to our findings in the infant.

It will be seen, therefore, that the differences between the fissures in adults and infants are slight and unimportant and that in both they show equally as marked variation in their point of origin, course and termination. Apparently this variability is dependent on no discoverable factors. We state this as the result of an attempt to establish some relationship between the anatomic characteristics of the chest and the location of the fissures. In this part of our study we investigated the following points in regard to the chest: (1) the general shape; (2) the anteroposterior and transverse diameters; (3) the circumference; (4) the subcostal angle; (5) the obliquity of the ribs, determined (a) at the spine and (b) in the midthoracic line. To these we added (6) the size of the liver (with special relation to the fissures of the right lung).

The result of this study was entirely fruitless and our conclusion is as stated above, namely, that these factors have no constant effect on the position of the fissures. We were somewhat surprised at this, as it would seem at first thought that the great difference between the shape of the chest in the adult and in the infant might readily influence the course and relationship of the fissures at the different ages. Apparently, however, the change in the shape of the chest goes *pari passu* with the development of the lung, with the result that the relation of fissure to rib or to interspace remains practically unchanged.

An important point is made by Dietlen,¹⁵ who calls attention to the fact that descriptions of the course of the fissures refer only to the relations at the surface of the lung, since the planes formed by the inward projection of the fissures through the lung traverse various lines. This is of some importance in operations on interlobar collections, although the perfection of Roentgen-ray technic has rendered so much aid in determining localized collections of fluid as to minimize the importance of other aids to diagnosis. This is especially fortunate since the normal relations of the fissures are profoundly modified by interlobar collections.

We have been impressed with the fact that students and interns usually disregard the position of the fissures and fail to take advantage of the aid which may be gained from observing their relations. For example, an area of dulness involving the region of the right apex and sharply following the line of the horizontal fissure of the right lung usually will prove to be croupous pneumonia or its delayed resolution, rather than a tuberculous pneumonia. Again, an area of dulness which follows and lies below the line of the oblique fissure usually will be due to a pneumonia rather than to a collection of fluid in the pleural cavity, or a tuberculous pneumonia; while the gradual extension of the border of dulness beyond the limits of the lower half of the oblique fissure will point to an empyema, rather than to the extension of a pneumonic process, as the latter is more apt to involve another entire lobe or large section of a lobe.

An interlobar collection of pus, following a pneumonia of either the lower or the upper lobe, would be apt to show an irregular extension of the dulness at some point beyond the line of the oblique fissure, usually about the middle of its course, but differing in outline from that caused by the gradual formation of an empyema on the one hand or of a spreading pneumonia on the other.

In thoracentesis a matter of practical importance is the selection of the point for exploratory tapping of large collections of fluid in the pleural cavity. The object in such a procedure is to penetrate the chest wall at a point where the lung has been pushed away so far that it will not interfere with the suction in the exploratory needle. When tapping is done with the vacuum apparatus for the actual withdrawal of fluid, or when the surgeon is seeking to establish permanent drainage, the lowest point of the cavity consistent with safety evidently is the optimum point of attack. With reference chiefly to adults the choice of the majority of authors is the sixth, seventh or eighth interspace between the midaxillary and postaxillary lines. In tapping more or less localized collections the area of greatest dulness usually is selected, for obvious reasons. It were well, however, to confirm such

15. Dietlen, Hans: *Ergebn. d. inn. Med. u. Kinderh.*, 1913, xii, 197.

choice by the evidence gained from stereoscopic plates and from the fluoroscope.

The lower part of the pleural sac (Fig. 2), that which lies between the chest wall and the diaphragm, is known as the costophrenic sinus, or complemental space of Burns. It lies below the lower level of the lung during quiet respiration and extends as far down as the tenth rib in the midaxillary line (Piersol¹⁴). Its function is to afford space for the expansion caused by deep inspiration, but even with the most extreme effort, in an adult, it is doubtful whether the lung ever expands sufficiently to completely fill the space.

In infants and young children this costophrenic sinus is subject to even less expansion than it is in adults, owing to the less vigorous inspiratory excursions of the former. This applies with special force to the right side, where the relatively large size of the liver causes the diaphragm to rise more abruptly to its dome. During quiet respiration, therefore, the lower limits of the pulmonary lobes form the

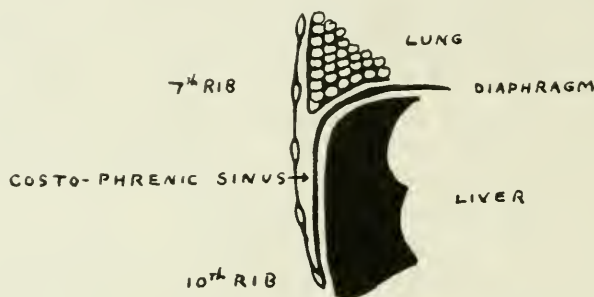


Fig. 2.—Diagrammatic sketch of the relation of liver and lung to the costophrenic sinus, in a frontal section made in the midaxillary line.

practical landmark of the lower limit of the pleural cavity, and the two layers of the pleura which line the costophrenic sinus lie almost in apposition.

When an empyema is present, this space is filled with pus, or, conceivably, may contain more fibrin than pus. While in the latter case the exploring needle might fail to reveal any fluid, the possibility of crossing the space and entering the diaphragm, and thus having a dry tap, is obvious. The serious consequences of traversing the diaphragm likewise are obvious, as on the right side the liver lies directly adjacent to the costophrenic sinus, separated from it only by the diaphragm, the parietal pleura and the peritoneum.

On the left side we found the upper border of the spleen, in the midthoracic line, lying opposite the ninth rib, or the interspace above or below it. In none of the bodies studied was the spleen greatly enlarged. Puncture of the spleen from a careless tapping through the

costophrenic sinus on the left side would be as liable to happen as would puncture of the liver on the right side. Increase in the size of the spleen naturally would increase the danger. A distended stomach also would lie directly underneath the costophrenic sinus, but unless the distention were extreme, would not lend itself easily to puncture.

We may say, therefore, that while the lowest level of the lung marks approximately the lowest level of the pleural cavity during quiet respiration, the optimum point for tapping the chest in infancy or early childhood should be somewhat higher than this level, in the interest of safe and conservative treatment.

According to Piersol¹⁶ the lower border of the right lung in adults reaches the eighth rib in the axillary line, and the eleventh rib, or a little higher at the spine. The lowest portion of the lung is in the axillary line or a little posterior to it, but the line thence to the spine is nearly horizontal. On the left side the course is practically the same, although the left lung may descend a trifle lower at the side. Posteriorly, the lower borders are very symmetrical. Piersol further draws attention to the variations found in different types of chests, which will be referred to later.

In locating the lowest level of the edge of the lung in infants, we have selected two lines, (1) the midthoracic line and (2) a line dropped vertically from the apex of the angle of the scapula "at rest." This point is readily palpated in the living child. The results were as follows:

The lower edge of the lung in the midthoracic line on the right side was at the seventh rib or seventh interspace (7 cases), eighth rib (7 cases); on the left side it was at the seventh rib (4 cases), eighth rib or eighth interspace (9 cases), ninth rib (1 case). In the line of the angle of the scapula the lower edge was at the ninth rib or ninth interspace (12 cases), at the tenth rib (2 cases); on the left side the lower edge was at the ninth rib or ninth interspace (9 cases), tenth rib or lower (5 cases).

As would be expected, these results show that the lungs in infancy do not, on the average, reach quite so low as in adult life and corroborate Piersol's statement that the left lung reaches slightly lower than the right. We find, therefore, that the extreme lower edge of the lung, measured in the midthoracic line, in many infants does not extend below the seventh rib, while in the line of the angle of the scapula, in an even larger proportion of cases, the lowermost limit is the ninth rib.

The size of the liver, however, had less effect than would be supposed, since in the five cases which showed the greatest enlargement

16. Piersol, George A.: *Human Anatomy*, J. B. Lippincott Co., Philadelphia, 1907, p. 1855.

of this organ the lowest point of the lung in the midthoracic line reached the eighth rib. Although in the case with the smallest liver the lowest level was recorded as being at the eighth interspace, in two others with livers somewhat below the average size, the lowest levels were found to be the seventh rib and the seventh interspace, respectively.

An obvious objection which might be raised to the practical value of these figures fixing the lowest level of the lungs is found in the age of the specimens we examined, for the reason that empyema and pleurisy are comparatively rare in those under 1 year of age. We found, however, that in the oldest infant, one of 15 months, the level in the right side was at the seventh rib in the midthoracic line, while the lowest level, the eighth interspace, was found in an infant of only 3 months. Excluding these, the average age in five cases, in which the lower margin of the lung was at the seventh rib, was $3\frac{1}{2}$ months, and in five others with the lower margin at the eighth rib, the average age was 3 months.

Since the costal, sternal and spinal diaphragmatic origins are fixed, and the development of the lungs and chest, as the child passes from infancy to adult life, is not only gradual, but also slow, it is probable that many children throughout the first decade will show the lowest level of the lung during quiet respiration at a point approximately as high as that found in some of these infants. The effect of deep inspiration at any age on the lower border of the lung of course is obvious.

In this connection we find that Piersol¹⁷ states that the relation of the lower border of the lungs to the ribs is rendered very inconstant by the varying inclination of the ribs in chests of different sizes and shapes. We investigated this point in our studies, but we could not determine any definite relationship between the obliquity of the ribs and the lower border of the lungs. The examination of our specimens gave the following results:

When the angle of obliquity of the ribs in the midthoracic line was from 55 to 60 degrees, the lower border of the lung in the midthoracic line was at the seventh rib or seventh interspace in four cases, and at the eighth rib in two cases. When the angle was from 60 to 70 degrees the lower border of the lungs at the midthoracic lines was at the seventh interspace in one case, at the eighth rib or eighth interspace in three cases. When the angle of the ribs was from 70 to 80 degrees, the lower border of the lungs in the midthoracic line was at the seventh rib or seventh interspace in two cases and at the eighth rib or eighth interspace in two cases.

17. Piersol, George A.: *Human Anatomy*, J. B. Lippincott Co., Philadelphia, 1907, p. 1856.

Although these figures indicate a tendency for the higher level of the lung to be found with the more vertical rib (55 to 60 degrees), the exceptions are too numerous to prove any definite relationship.

It would seem that the lowest point for tapping with absolute safety, therefore, would be the fifth or possibly the sixth interspace in the midthoracic line and the seventh or possibly the eighth interspace in the line of the angle of the scapula. In the authors' clinical experience it might be said that the sixth or seventh interspace in the postaxillary line (which lies between the line dropped from the angle of the scapula and the midthoracic line) is the optimum point of attack.

CONCLUSIONS

1. The fissures of the lung in infancy show practically the same relation to the bony framework of the chest as in adults.

2. The origin, course and termination of the fissures vary greatly in different individuals.

3. The variations apparently do not depend on any of the anatomic characteristics of the chest and cannot be predicted therefrom.

4. The lower level of the lungs in infants and probably in young children does not extend quite so low as in adults.

5. For this reason, and owing to the anatomic characteristics of the bases of the pleural cavities in early life, great care should be exercised to avoid damage to the diaphragm in performing thoracentesis.

6. The sixth interspace in the midthoracic line and the seventh or possibly the eighth interspace in the line of the angle of the scapula (at rest) represents the lowest limits of absolute safety for thoracentesis in early life.

FRESH AIR IN PEDIATRIC PRACTICE *

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There is an agent of wonderful power and value to the pediatrician, the use and action of which is little appreciated even by the more prominent in the pediatric community. It has, therefore, seemed to me worth while to speak of its method of action and of its application to the uses of the pediatrician. I refer to fresh air.

By fresh air as a therapeutic agent I mean moving and cool outdoor air. The still air of the hot, humid dogdays of summer is little better than that of the crowded, hot room in winter. Fresh, moving, cool, outdoor air stimulates the appetite, induces quiet sleep, brings color to the cheeks, and increases the resistance of the organism to infection.

In seeking an explanation of the action of fresh air on the human body we find the claim that fresh, cold air raises materially the blood pressure. This claim, however, has not been confirmed by subsequent investigation, and we seem driven to the position that the favorable action of fresh air on the organism is due to the absence of the deteriorating effects of closed rooms. In fresh air the body has the advantage of normal conditions, while any modification of these, from a room with the windows partially open to a closed room, or to the conditions in the Black Hole of Calcutta, furnishes increasingly serious results from air stagnation.

The idea that air which had been breathed by other people was unhealthful probably arose from the unpleasant odor of closed and crowded rooms, and from symptoms elicited by extremes of this sort. The symptoms produced by closed places are depression, headache, dizziness, nausea, perspiration, thirst and difficult breathing. The elements producing these results were supposed to be a diminution of the oxygen and an increase of the carbon dioxid, with the possible appearance in such an atmosphere of a really poisonous product from the expired air. Experiments, however, have for the most part discredited this theory. The amount of oxygen in crowded, closed rooms is not depleted to a danger point, nor is the amount of carbon dioxid increased to such a point. Efforts to find a poisonous element in such air have

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been made from time to time with negative results. In 1911 Rosenau and Amoss¹ carried out a series of experiments on guinea-pigs to demonstrate this, but subsequent work by Weisman failed to confirm their results, and Lee² states "that it may be regarded as finally settled that expired air contains no volatile, toxic, organic constituent."

In 1883 Hermans³ of the Hygienic Institute in Amsterdam became convinced of the error of the oxygen and carbon dioxid theory, and found that his own temperature was raised in crowded assemblages from three-fifths to more than a degree Fahrenheit; he concluded that the discomfort of crowded places was due to inability of the body to cool itself in a hot, moist atmosphere.

Flugge's⁴ experiments in 1905 really showed the condition that produced the symptoms elicited by enclosure. He put a subject in a closed box until symptoms appeared and then allowed him to breathe, through a tube, air from the outside, without any relief of his symptoms. Another subject, outside the box, on breathing the air from the inside had no symptoms. This showed that the discomfort of a closed place has nothing to do with the air we breathe, but with conditions of the skin brought about by such confinement. We suffer in crowded, unventilated places through lack of function of the skin, rather than through respiratory embarrassment. Recent experiments have demonstrated more directly the nature of this embarrassment, for if an electric fan is placed in the corner of the box and air in the box is put in motion the symptoms disappear immediately.

These symptoms then are due to stagnant, hot, moist air surrounding the body. They may be produced in such an enclosed experimental box; they may be produced in an auditorium, overheated and crowded with people, or in a tightly closed living-room with few people, but no moving air, and such symptoms will be accentuated in people wearing heavy, impervious clothing that prevents access of moving air to the skin. It is evident, then, that we should wear as little clothing as is consistent with comfort. Most of us could wear much less clothing than we are accustomed to wearing.

The result of these elaborate observations is in brief that fresh air is good, not because it supplies oxygen, not because it is not overloaded with carbon dioxid, not because it contains no poisonous element, but because it allows the body to exist under such circumstances that it can control its moisture and temperature.

In the application of these newly developed facts to our daily work in pediatrics we have to combat the traditional fear of drafts and the

1. Rosenau and Amoss: *Jour. Med. Research*, 1911, xxv, 35.

2. Lee: *Jour. Am. Med. Assn.*, 1914, lxiii, 1625.

3. Hermans: *Arch. f. Hyg.*, 1883, L, 1.

4. Flugge: *Ztschr. f. Hyg.*, 1905, xlix, 363.

habit of many people of living in close, hot rooms. It is only on account of the general acceptance of the brilliant results obtained in certain diseases, notably pneumonia and tuberculosis, by the use of fresh air, that we are able oftentimes to obtain the fresh air for our children which they need for the preservation of health and their proper development. Equally brilliant results possible in other diseases are not known by many physicians.

I believe that the cold air of winter is much more stimulating and produces better results in children than the mild air of spring and autumn.

Dr. Ellsworth Huntington of Yale,⁵ in a very careful and interesting study of the influence of climate on civilization, concludes that spring and autumn are the periods of greatest mental and physical activity. This is contrary to the inferences I have drawn from my experiences with the influence of outdoor air and I find that his results are obtained from activities which are housed during the winter, that is to say, college students, factory workers, etc. These people are all housed in winter and live in warm air and thus are little affected by the tonic action of cold outdoor air. In spring and autumn, on the other hand, the windows are opened. If he had used outdoor occupations for his studies I believe his results would have been different.

The best results from fresh air are obtained by keeping the children out of doors day and night, and we have no healthier children than those who, having suffered in early life from tuberculous infection, have been kept for years out of doors. These children are not subject to colds which others have during the winters; they have good color, good appetite and a normal, robust development.

Many of our pediatricians have confused fresh air with cold air, and one may see in hospitals cold wards and warm wards. Such cold wards are probably better than warm wards, but they lack altogether the free, moving air which is the great advantage of the outdoor ward, and often the sunshine, which we know to be one of the most potent of our therapeutic agents.

Outdoor sleeping porches enclosed on three sides and roofed, but open to the south, furnish the best fresh air at night, while in the daytime balconies and rooms without heat and windows wide open supply the air we need.

It is evidently not enough, however, that we should have this fresh air, but we should also look to the clothing to see that our children are not sealed in with heavy, impervious covering so that the skin is unable to rid itself of the heat and moisture.

5. Huntington, Ellsworth: *Civilization and Climate*, Yale University Press, 1915.

The experiments I have reviewed show us how it might not be impossible for a child out of doors, in cold weather, to be embarrassed by such clothing.

Where it is impossible to obtain such complete outdoor exposure, the best substitute in cold weather has seemed to me to be in rooms with cheesecloth screens in the windows. Such cheesecloth screens should cover all the space available when the windows are opened. They allow a moderate access of air without the presence of the much-feared drafts. The objection is that they allow less sunlight than glass, but this disadvantage is more than counteracted by the quality of the air of the room.

Other methods of ventilation consist in patent ventilators put under the lower sash. These, however, allow more movement in the air of the room, but less open space, and some of them furnish no filtration of the dust from the air.

The greatest blight on the fresh air movement of the day is the vogue of elaborate, mechanical ventilating systems, which obtain the air from the basement, pump it through flues into and out of the rooms. Such systems are very expensive, occupy a great deal of space, and while the air furnished may be sufficient for the preservation of life, it often lacks the freshness and invigorating character of the air obtained from open windows or through cheesecloth screens. The worst phase of the current ventilating systems is when they prohibit the opening of the windows. Under intelligent operation they may prove efficient. Closed rooms favor the conveyance of disease from one person to another, and our ventilating systems make practically no provision for carrying off germ-laden dust. There is little conveyance of disease in outdoor school classes or outdoor hospital wards.

The danger of housing is not alone in the bad air of a closed room, but to a susceptible organism it consists also in the sudden change from a temperature of 70 or 80 in a dry room all night to a temperature perhaps of zero, with a cold north wind blowing out of doors, then to a heated auditorium, with a saturated, moist temperature of 80, and again out into zero weather. It is only during the existence of marked changes of temperature between indoors and outdoors that epidemics of colds exist, for during the summer we have practically an immunity to colds and colds occur only when our houses are closed.

In New York our epidemics of colds usually begin in November and December, while in New Hampshire, where I often spend my summers, cold weather inducing people to heat their houses often occurs in September, and it is not uncommon for the neighboring town to have a severe epidemic of colds at such a time. In the summer

time the air is less invigorating, but there is the advantage of less sudden change from cold to hot or from dry to moist air.

Much is heard of the superiority of country air over city air, but recent investigations have shown but little difference in its chemical composition, and if the children are kept in the open air, as they should be in the city, they are much healthier than most country children.

Night outdoor air, while it is not so good as day air because it lacks the beneficent effect of sunlight, is far superior to night air in the house, and the advantage of fresh air treatment is reduced by half if children are housed at night.

A statement as to the diseases to which fresh air treatment is applicable is much more difficult than a statement of the diseases to which it is not applicable. I will, therefore, first enumerate the conditions to which fresh, cold air has not been demonstrated as practicable.

Premature infants who show a subnormal temperature in cool air should be kept at an air temperature that will preserve the normal body temperature. This warm air, however, must be a freely moving warm air, rather than the dead air found at the bottom of a box. On this account, for such babies, a properly constructed incubator is far superior to the substitutes that are often adopted.

I am not sure whether such cold, fresh-air treatment is applicable to children with kidney lesions or with severe heart lesions, although I have seen children with severe endocarditis who preferred to be out of doors in winter rather than in closed rooms, and I have seen no injury from such exposure.

The most important application of this fresh-air treatment is to build up the vitality and resistance to disease of frail children, and in this sphere, I think, it shows perhaps its most brilliant results. This is true in early life, for children with marasmus and malnutrition who are impossible to feed so as to obtain an increase in weight will often gain promptly, with no change in food, on being kept out of doors or in front of an open window in winter. I have seen many children who have reached that stage of malnutrition that usually precedes death, with a dusky hue of the face, react to such treatment and recover entirely.

Another condition of early life, rachitis, is, I believe, entirely a disease of housing. It exists, not in tropical climates where people live out of doors, but in colder climates where people house themselves in winter. The symptoms develop in winter only and the severe cases that we see are entirely confined to the children of races that have been accustomed to warm climates where the families do not house themselves in winter. This susceptibility is not confined to human beings, but exists equally in the lower animals. Animals brought here

from tropical climates develop a disease that is in many respects similar to our rachitis and which is known in zoological gardens as cage-disease, and this is the fatal disease that all zoological gardens have to combat and from which none will be free until greater care is taken to supply these animals with fresh, cool, moving air in winter. On account of this susceptibility Italians and colored people and other people accustomed to tropical climates should be warned that they must give their children fresh air in winter if they would have them survive and develop properly.

In all the acute infectious diseases I think there is now a general acceptance of the advantage of fresh air, excepting perhaps in measles and scarlet fever. In tuberculosis there is now no question of its advantage. In pneumonia the results from this treatment have exceeded those from any other method of treatment, including specific treatment with serums and vaccines. There are still many men, however, who, while allowing that fresh air is beneficial in an inflammation of the lung, doubt its efficacy in bronchitis, pharyngitis, laryngitis, rhinitis and otitis. The only reason why such men doubt its efficacy is because they have not sufficiently tried it. I have used it in all these conditions and I believe that it is of direct benefit and that it diminishes materially the mortality.

I have convinced myself also that measles and scarlet fever are no exceptions to the rule, and I have put patients during a severe measles epidemic complicating scarlet fever out of doors in winter without a single fatality, although some of the scarlet fever patients were exceedingly sick when the change was made. The change to outdoor air seemed to help them all. Among these cases was one of scarlet fever in which from a breaking down of the lymph nodes there was a large ulcer extending from one side of the neck to the other. Under the influence of the cold air the neck healed with a linear scar. It is equally unnecessary in measles to darken the room. We should let children with this disease have all the sunlight that their eyes will bear, as well as cold, fresh air.

In connection with the healing of this surgical condition complicating scarlet fever, the statements made by H. S. Soutter⁶ are of interest. He says that they received wounds that were soiled by earth, manure and fragments of cloth covered with mud and that there was one way by which all such infections may be defeated, by plenty of fresh air or oxygen. In several cases, in which the wounds were so horribly foul that it was impossible to tolerate them in the wards, the patient was put in the open air with the wounds covered only by a thin piece of gauze. The results were almost magical. The wounds lost their

6. Soutter, H. S.: A Surgeon in Belgium. 1915.

odor and began to look clean, while the patient lost all signs of the poisoning which had been so marked before. He thinks this treatment may account for the fact that they had no case of tetanus.

J. W. Markoe states his experience with open-air treatment in sepsis at the Lying-In Hospital in New York. Of fifty-seven patients treated indoors, two left the hospital and fifty-five died; that is, all the patients who remained in the hospital died; while of fifty-three patients who were put out of doors, twenty-two, or 41 per cent., recovered.

The common colds of winter are favorably influenced by cold, fresh air, as are other forms of infections.

In diseases characterized by abnormal conditions in the blood, such as simple anemia, von Jaksch's anemia and leukemia, I believe there is a large field of usefulness for this treatment, and I have myself, in a very limited number of cases, obtained quite brilliant results.⁷ These observations must, however, be confirmed by many more before one can consider this claim as proved. Markoe, however, states that patients with anemia from severe hemorrhage are greatly benefited by fresh air.

Before closing, it would seem that some explanation is due as to why, if all these statements are true, children are still housed and many adults have a panic if a breath of cold air strikes the back of their necks or their bald heads, while children who are brought up without fear of cold enjoy it wherever it strikes.

The supposed production of catarrhal inflammations in adults by exposure to cold air, if it really exists, exists only on account of suggestion. These people have been brought up to such a fear of fresh air that every infection of the upper air passages to which they succumb they attribute to this health-giving influence. It is sincerely to be hoped that many of the coming generation may be brought up under different ideas and may be less dependent on hot, offensive, stagnant air for the supposed comforts of life.

There is evidence enough to show that many diseases are favorably influenced by this simple and safe measure. Why do you not use it? Some are afraid, some will not take the trouble. Many children are allowed to become sick from housing and children may be seen dying in closed wards of many of our best hospitals who might have been saved had they been put out of doors.

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7. Freeman, R. G.: *Am. Jour. Med. Sc.*, 1916, cli, 1.

CLINICAL DEPARTMENT

A CASE OF INFANTILISM DUE TO HYPO-PITUITARISM*

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For centuries the pituitary gland has been one of the most mysterious structures of the human body; some have considered it the seat of the soul, others have looked on it as a rudimentary organ, while most physiologists have confessed total ignorance as to its functions in the human economy. The discovery in 1886 by Pierre Marie of the association of changes in the structure of this gland with acromegaly has stimulated further and detailed studies of the physiology of the epiphysis, and it was found that it is endowed with a number of vital functions, such as regulation of blood pressure, contraction of smooth muscle, particularly the uterus; the sexual functions, and the growth of connective tissue and of the skeleton. Moreover, it was found that the pituitary has a great influence on the mentality of its possessor.

Among the pioneers in the study of the physiology of the pituitary may be mentioned Frankel-Hochwart, Froelich, Cushing, Vincent, Cyon, and others. But it appears that there remains much yet to be learned about this organ.

One of the most interesting phases of the study of the pituitary function is its relation to infantilism, a syndrome which has been obscure for centuries. E. J. Mullally,¹ A. W. Hewlett,² George E. Rennie³ have reported cases of infantilism with pathologic changes in the pituitary gland found at necropsy. The case here reported appears to belong to this class, because the symptoms pointed undoubtedly to the infantilism being due to perversion of function of the pituitary.

The patient, Y. K., a girl 12 years old, was born in this country of Russian-Jewish parentage. The mother gives a history of two miscarriages and the fact that she is markedly prognathous, her jaws protruding like a muzzle, may be suggestive. On the father's side there is a history of tuberculosis. It is also noteworthy that the mother, sisters and brothers are of unusually large size, especially when we bear in mind that they are Jews who are

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* From the Neurological Division of the Mount Sinai Hospital Dispensary.

* Case presented before the New York Neurological Society, June 6, 1916.

1. Mullally, E. J.: Arch. Int. Med., 1913, xi, 523.

2. Hewlett, A. W.: Arch. Int. Med., 1912, ix, 32.

3. Rennie, G. E.: Brit. Med. Jour., 1912, i, 1355.

ethnically of low stature. Repeated Wassermann examinations of the blood from the mother and child proved negative. A von Pirquet inoculation also gave negative results. No forceps were used during the delivery of the patient. She was breast fed and, according to the mother's statement, began to walk at 2 years of age. At the age of 18 months the child suffered from whooping cough.

When the infant was 2 years of age the mother was rather alarmed at its stunted growth and applied to a hospital for treatment. She tells me that the powders given to the child were quite effective at the time, but unfortunately I am unable to ascertain the nature of the medication.



Fig. 1.—Photograph of patient suffering from hypopituitary infantilism.

When the child was brought to me on March 5, 1916, the mother pleaded for relief, stating that although the child is rather cunning and shrewd, she is backward in her studies at school. Moreover, the mother complains that the child is not promoted in the school because of her stunted size. No history of frequent micturition or of enuresis is obtainable.

The patient appears the size of a child of 4. The face and mucous membranes are pale, the hair fine and scanty. The subcutaneous adipose tissue is rather excessive, but the skin can be raised in folds. The abdomen is protruding, and the umbilicus is situated lower down as is the case in the infantile type.

Examination of the cranial nerves gives negative results, excepting the optic disks, which are pale, but there is no change in the visual fields and

the acuteness of vision is normal. The reflexes are normal, and no sensory changes could be discovered. The neck is well formed, the thyroid is not palpable. Nothing of significance could be ascertained by an examination of the lungs. The urinary findings are negative.

The following table gives some anthropometric data about the little patient:

Weight	46 lb.
Height	98 cm.
Lower extremities	46 cm.
From anterosuperior spine to upper border of the patella.....	25 cm.
From upper border of patella to internal malleolus.....	21 cm.
Upper arm (from acromion to tip of olecranon).....	17.5 cm.
Lower arm (from olecranon to styloid process of the radius).....	14 cm.
Distance between anterosuperior spines.....	24 cm.
Circumference of the chest	59 cm.
Circumference of the abdomen	63 cm.

No striking asymmetries have been found.



Fig. 2.—Roentgenogram of the skull of the patient, showing a sella turcica encroached on by bony projections from its anterior and posterior clinoid processes, as well as from the base. Note the thinness of the frontal and parietal bones.

The radiographic findings (Fig. 2) show an encroachment on the cavity of the sella turcica by bony projections from the anterior as well as the posterior clinoid processes, also projections from the base of the sella. The entire skull is very thin and the frontal and parietal bones show a peculiar mottling, while the anterior fontanel is not completely closed. There is also lack of ossification of the long bones (Fig. 3).

Several times glucose was given to the patient while on a fasting stomach running up from 50 to 200 gm., and no sugar was found in the urine at any

time, thus showing the high sugar tolerance. Five drops of a 1:1,000 solution of epinephrin were given hypodermically, and no sugar was obtained in the urine.

Examination of the blood shows the following results: Hemoglobin, 60 per cent.; erythrocytes, 3,500,000; white blood cells, 6,000. No abnormal cells, and the cell count was negative. The results of a lumbar puncture were negative.

The Binet-Simon test shows that the child has the intelligence of one 7 years old. She is, however, very poor in arithmetic. She can count correctly, but



Fig. 3.—Roentgenogram of hands and forearms of patient, showing defective ossification.

finds difficulty in counting backward. Addition and subtraction of small and simple numbers she does not perform with ease or correctly most of the time.

For about a month the child was fed on thyroid extract. Various doses were given, beginning with $\frac{1}{16}$ of a grain to 1 grain without any noticeable changes. Then pituitary extract was administered (the entire desiccated gland). At the end of a month an increase in weight of half a pound was found. At

the end of three months, one pound increase, the child now weighing 47 pounds. No increase in the size of the child was as yet noticed.

Considering the conclusions arrived at by E. A. Schaffer,⁴ to the effect that the anterior lobe is probably responsible for the growth of the body, we may rightly call into question the old theories of Loraine, Brisaud, and Sanct de Sanctis concerning the nature and origin of infantilism. Loraine thought that all forms of this condition were due to infections. This is, of course, a vague term and can easily be dismissed at the present state of our knowledge of the physiology and the pathology of the pituitary. The thyroid was held responsible for infantilism by Brissaud, while Sanct de Sanctis thought the condition due to pluriglandular disturbances.

The roentgenogram, as well as the clinical findings of this case, point to the pituitary being primarily responsible for the stunted growth. Whatever thyroid involvement there is may be due to the usual response of this gland to changes in the pituitary.

SUMMARY

Our patient presents undoubtedly the syndrome of infantilism caused by a hypofunction of the pituitary. Our reasons are the following:

The bony projections in the sella turcica must of necessity interfere with the function of the pituitary by the pressure it exerts on this gland. On the other hand, should we assume that the bony projections are of embryologic origin, it is clear that, even so, the pituitary was hindered in its development.

The high sugar tolerance, both to glucose and to epinephrin, the lack of ossification of the long bones, the anemia, the absence of distinct myxedematous symptoms and signs, lead us by exclusion to the pituitary for the cause of the stunted growth.

This case, with the above mentioned cases, tends to prove that infantilism is in all probabilities due to hypofunction of the pituitary gland.

252 East Broadway.

4. Schaffer, E. A.: *Proc. Roy. Soc. Med.*, lxxxi, 442.
lxxxi, 442.

TRANSIENT ABDOMINAL TUMOR IN A CHILD OF FIVE YEARS WITH REDUNDANT COLON *

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AND
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The complaint in this case was the periodic occurrence of abdominal tumor. The patient was the only child of young and healthy parents, though the mother might be said to be of a nervous temperament. The birth weight was 11¼ pounds and the labor was tedious, though a head presentation, delivery being finally effected, after forty-eight hours, by instrumentation. No difficulty was experienced, however, in establishing respiration, and the infant was normally nourished until two days after birth, when a promising lactation for some reason failed. After this the child ran the gauntlet of proprietary foods, including Eskay's, Mellin's and finally Horlick's malted milk, which was continued well into the second year. He sat up at five months, began the eruption of teeth at eight months and walked at nineteen months. With the exception of frequent attacks of rhinitis, to correct which an adenoid operation was performed at the age of 2½ years, the patient escaped all of the diseases peculiar to childhood, progressing in a fairly normal manner to the age of 3½ years.

In December, 1914, approximately a year before my first examination, the patient became suddenly ill in the night, with an attack characterized by extreme nausea and severe vomiting and the appearance of a rounded tumor in the hypogastrium, simulating a distended bladder. The vomiting, to judge from the description, was simply bile-stained gastric juice and at no time stercoraceous. The tumor was elastic, but not especially tender to touch. There was no history of previous disturbance in the regularity of the bowel, as to constipation or diarrhea. Fever was not present.

The physician called at the time had evidently made a diagnosis of intussusception and had completed plans for an immediate removal to the hospital for operation. Returning a few hours later for the patient, he had been, as could be well imagined, much surprised to find that the mass had spontaneously disappeared and the patient recovered.

After this initial appearance these attacks had recurred at varying intervals, seldom less than three weeks and on several occasions as long as six weeks. They had varied in the severity of associated symptoms and likewise in duration, seldom, however, lasting over two days. The tumor had invariably appeared first over the region of the bladder, sometimes larger, sometimes smaller, moved about the abdomen spontaneously and finally disappeared. Its appearance had always been associated with nausea and vomiting, and its disappearance with a pronounced paroxysm of abdominal pain. Following the first attack there had been some tendency to constipation, but the bowels had been kept freely open by the daily employment of mineral oil by mouth. The diet had been well regulated and in the intervals the patient had quickly recovered lost weight. Ordinarily the child was quite normal, played actively and appeared in good health. No prodromal symptoms had been observed.

At the time of my first examination, I found the patient in bed lying on his back, thighs partially flexed. The attack was several hours old and there was

* Submitted for publication May 29, 1916.

* Read at the Twenty-Eighth Annual Meeting of the American Pediatric Society, held at Washington, D. C., May 8-10, 1916.

still some nausea. Presenting in the hypogastrium was a smooth tumor about the size of an orange, elastic, but not tender to touch, and dull on percussion. It was palpable by rectal examination and suggested strongly a distended bladder. The mass was, however, freely movable, it being possible, without undue force, to manipulate it about the entire abdomen. There was a fairly well-pronounced beading of the ribs. The pulse was rapid, but regular. The temperature normal. A leukocyte count gave 11,500. The von Pirquet and Wassermann tests were negative. No further significant facts were observed.



Fig. 1.—Roentgenogram taken tenth minute after bismuth flow commenced.

Under restricted feeding and large enemas slowly administered, the mass spontaneously disappeared. An examination of the abdomen subsequently was absolutely negative.

Through the courteous cooperation of Dr. J. H. Selby, a very thorough Roentgen study of the case was made between and during attacks. In this connection I believe that I cannot do better than read Dr. Selby's own report. Examination was made March 5, 1915:

"Findings: Original plates, both back down and face down before the bismuth enema, were negative. Twelve ounces of suspended bismuth subcarbonate were injected by gravity and the visualized filling observed. Plate records were made at the second, fourth, seventh, tenth and thirtieth minute after the flow commenced. The ampulla filled normally, the bismuth column passing vertically, almost in a straight line, to the level of the second lumbar, slightly to the left of the midline, where it turned sharply downward a distance of six inches to the left iliac fossa, at which point it turned sharply on itself



Fig. 2.—Roentgenogram taken at twenty-fourth hour after bismuth enema.

passing upward to the diaphragm, when it again turned on itself and descended at a posterior level for three inches before crossing as the transverse colon at the second lumbar. The hepatic flexure is on a level with the transverse colon. The cecum occupies a position one inch above the right iliac crest. The bismuth column reached the cecum in six minutes. *By manipulation the redundant sigmoid or distal portion of the colon can be made to swing over toward the right side and back to the left at will.*

"At the twenty-fourth hour there is considerable bismuth residue in almost the entire colon. The aforesaid redundant colon is distinctly outlined.

"Examination made March 27, 1915:

"Findings: A tumor mass the size of a large orange is palpated in the right upper quadrant. The bismuth injection showed the mass to be redundant descending colon. Visualized palpation reduced the tumor."

CONCLUSIONS

The clinical history, in the light of the Roentgen-ray findings, would seem to justify the assumption that the phantom tumor was the result of a temporary kinking of the redundant colon (or sigmoid), incident to its displacement to the right, which was followed by either fecal or gaseous distention in the loop. When the loop filled itself to a certain point, it swung gradually to the left and automatically unkinked itself, with a disappearance of the tumor mass.

CONGENITAL OBLITERATION OF THE AORTA

WITH REPORT OF A CASE *

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Congenital obliteration of the aorta occurs in two main forms: closure at the orifice, so-called atresia ostii aortae; and at the isthmus, referred to as coarctation.

These two forms present different clinical aspects. Coarctation is of greater frequency. Abbott¹ states that over 200 cases have been reported. This lesion occurs in that part of the aorta lying between the left subclavian artery and the insertion of the ductus arteriosus. Patients having this anomaly may reach adult life. Recently LeCount² demonstrated a specimen removed from the body of a man 42 years old. The greatest age reached occurred, in an instance recorded by Reynaud, cited by Hochsinger,³ in which the patient was 92 years old. The clinical signs, as summarized by Hirschfelder,⁴ are difference in the size and quality of the pulse in the upper and lower extremities; difference in the blood pressure in the upper and lower extremities; a low murmur over the arterial trunks, frequently at the angle of the left scapula, and the presence of large tortuous mammary, thoracic and scapular arteries. As to the etiology, Martens⁵ gives three causes: the influence of traction exerted on the isthmus by the ductus arteriosus, especially during its involution; changes in the vessel wall analogous to an endarteritis fibrosa, first suggested by Thoma; a congenital malformation of the vessel, the latter view being supported by the frequent concomitant occurrence of other congenital abnormalities, which have been noted in 38 per cent. of the recorded cases.

Atresia ostii aortae is less common. This lesion occurs at the orifice of the aorta. Humphry⁶ cites Rauchfuss, who collected twenty-four cases. Patients with this abnormality generally do not live more than a few weeks. In an instance recorded by Bardeleben and cited by Martens, the age of 27 weeks was reached. This lesion is generally

* Submitted for publication July 1, 1916.

* From the Department of Pathology, Michael Reese Hospital.

* Read before the Michael Reese Clinical Society, Jan. 3, 1916.

1. Abbott, Osler and McCrae: *Modern Medicine*, 1915, iv, 399.

2. LeCount: *Tr. Chicago Path. Soc.*, 1914, ix, 88.

3. Hochsinger: In Pfaunder and Schlossman, *Diseases of Children*, iii, 474.

4. Hirschfelder: *Diseases of the Heart and Aorta*, 1913, p. 547.

5. Martens: *Virchows Arch. f. path. Anat.*, 1890, cxxi, 322.

6. Humphry, Allbutt and Rolleston: *System of Medicine*, 1909, vi, 286.

associated with aplasia of the left ventricle and very frequently other abnormalities, which lend support to the view that it is a congenital malformation. Monkeberg⁷ recognizes an inflammatory type. He records an instance of a patient four days old, born spontaneously after a normal labor. He bases his view on the results of the study of microscopic sections.

Our specimen of congenital atresia of the aorta at the orifice was encountered in a routine postmortem examination.

CASE REPORT

History.—The infant boy was born in the maternity section of the Michael Reese Hospital, Oct. 17, 1915, a patient of Dr. Braude. The mother was a primipara, who had passed through an uneventful pregnancy. Labor had been normal and delivery spontaneous. The child appeared to be well formed and presented no external abnormalities. The heart sounds were normal; no murmurs were heard, the cry was normal, the skin was clear and of good color. On the second day the child was put to the breast, and apparently nursed normally. On the third day it suddenly became cyanotic, went into convulsions, and died within a few hours.

Necropsy.—The anatomic diagnosis was: congenital atresia of the aorta at the orifice; total absence of the aortic valves; hypertrophy of the left ventricular wall; dilatation of the right ventricle; common opening of the coronary arteries; partial apneumotosis of the lungs; multiple small hemorrhages in the epicranium, pericardium, liver, kidneys, thymus and suprarenals; marked passive congestion of the liver, spleen and kidneys; uric acid infarcts in the kidneys; cloudy swelling of the liver; hydrocele; adherent umbilical cord.

The body was that of a well-nourished white infant boy, measuring 48 cm. in length and weighing about 7 pounds. Rigor mortis, algor mortis and postmortem lividity were present. The anterior and posterior fontanels were open, and the bones of the skull were movable at their sutures. The pupils were slightly dilated, equal in size, the corneas were clear, the nose was well formed. The chest and abdomen appeared normal externally. The proximal end of the umbilical cord was adherent, measured 4 cm. and was dried and atrophied. The scrotal sac was slightly enlarged and contained clear serous fluid. The costochondral junctions and the ends of the long bones appeared normal.

The body was opened by the usual longitudinal incision. The subcutaneous adipose tissue was normal in amount. The peritoneum was smooth, glistening and transparent, and there was no free fluid in the peritoneal cavity. The liver extended 5 cm. below the costal arch, the stomach was slightly distended and the appendix appeared normal.

The heart lay free in the pericardial sac, which contained the usual amount of clear serous fluid. It was slightly enlarged, measured 37 mm. from the apex to the base, and weighed 23 gm. The apex was made up of the right ventricle, which was appreciably larger than the left ventricle. The auricles and the coronary sinuses were distended with blood. Beneath the visceral and parietal pericardium there were multiple small hemorrhages. The heart was opened by two incisions into the ventricles parallel to the interventricular septum. The right ventricle was dilated and measured 40 mm. transversely and 33 mm. from its most dependent point to the pulmonary artery. The ventricular wall was 3 mm. wide. The pulmonary artery was considerably larger than the aorta; exposed and laid open, it measured 25 mm. along the line of the valve attachment. The valves of the pulmonary and those of the tricuspid opening appeared normal in structure. The left ventricle was considerably smaller than the right; it measured 10 by 11 mm. The lining endocardium was

7. Monkeberg: Deutsch. path. Gesell., 1907, xi, 224.

smooth and glistening. The left ventricular wall was hypertrophied, and measured 10 mm. The mitral opening was smaller than the tricuspid opening, was made up by two valves, which did not approximate well, but which were otherwise well formed. From the ventricular cavity there was no opening into the aorta; but at the site of the aorta there was a small pinpoint retraction of the endocardium, and there was no evidence of the aortic valves. The aorta was completely closed for a distance of 2 cm.; beyond this point it dilated and reached its normal diameter at the junction of the ductus arteriosus. The closed aorta was 2 mm. wide. The coronary arteries opened into the left ventricular cavity by a common orifice near the site of the aorta close to the interventricular septum. The right auricle was slightly dilated, but normal in structure; the left auricle was smaller than the right and presented no abnormalities. The ductus arteriosus and foramen ovale were widely patent.

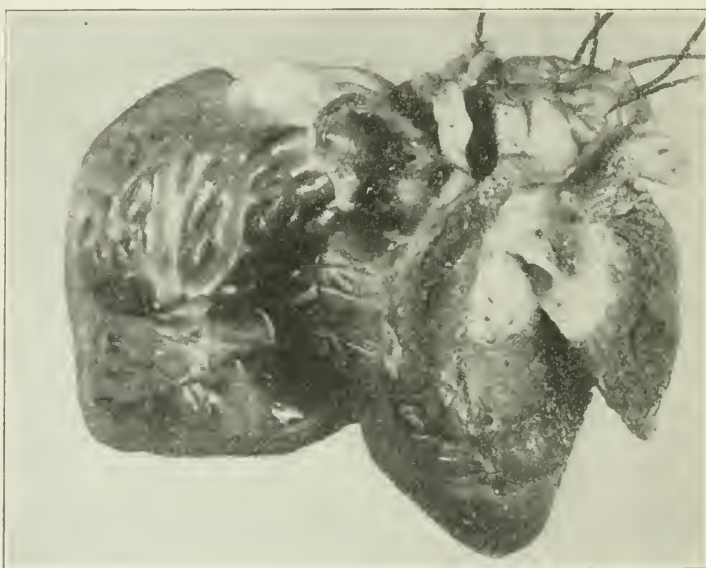


Fig. 1.—Photograph of heart, anterior surface, dissected.

The lungs lay free in the pleural cavities. The right lung was normal in size, weighed 30 gm., was pinkish red in color, and floated low in water. It was soft and friable, except a few small areas which were firm and deep red in color. Sections of these areas sank in water. From the freshly cut surface a frothy hemorrhagic fluid escaped. Beneath the pleura and in the substance of the lung there were multiple small pinpoint hemorrhages. The left lung weighed 28 gm. and also contained small hemorrhages.

The thymus was dark red in color, weighed 7 gm., measured 4 by 3 by 1 cm., and contained numerous small hemorrhages.

The liver was enlarged, was dark red in color, measured 11 by 6.5 by 5 cm., and contained numerous subcapsular hemorrhages. The lobular markings were distinct. From the freshly cut surface of the liver dark fluid blood escaped; the surface appeared dull, and the edge everted. The gallbladder contained about 3 c.c. dark green, tenacious fluid.

The spleen was normal in size, weighed 10 gm., was congested, and the cut section was dark red in color.

The right kidney contained numerous small subcapsular hemorrhages. It was normal in size, fetal lobulation was present, and it measured 4 by 3 by

2 cm. The capsule stripped easily, leaving a smooth, shiny surface. On cut section, the cortex appeared dull, the medulla was intensely congested and at the pyramids there were several yellowish-white uric acid infarcts. The left kidney presented the same alterations.

The head was opened, the brain removed and sectioned. There were multiple small hemorrhages in the epicranium, but otherwise there were no abnormalities.

As this infant lived several days extra utero, besides passing through its normal intra-uterine life, some explanation of the circulation should be forthcoming. In the normal fetal circulation (Wil-

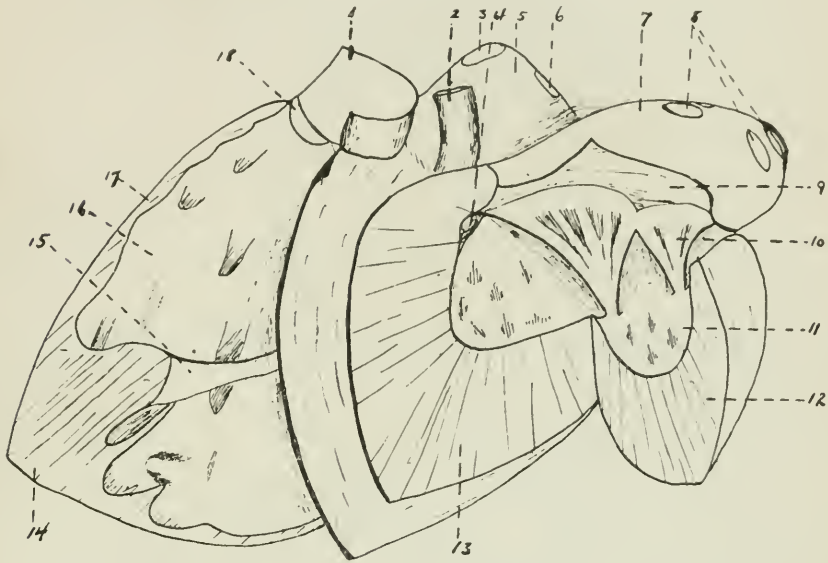


Fig. 2.—Sketch of anterior surface of the heart corresponding to photograph shown in Figure 1. 1, pulmonary artery; 2, aorta; 3, superior vena cava; 4, common opening of the coronary arteries; 5, right auricle; 6, inferior vena cava; 7, left auricle; 8, pulmonary veins; 9, mitral orifice; 10, mitral valves; 11, left ventricular cavity; 12, left ventricular wall; 13, interventricular septum; 14, apex of heart; 15, large papillary muscle of right ventricle; 16, right ventricular cavity; 17, right ventricular wall; 18, pulmonary valves.

liams⁸) the blood from the superior vena cava enters the right auricle, passes into the right ventricle, then into the pulmonary artery, where it divides, some passing into the pulmonary circulation, the greater part passing through the ductus arteriosus into the descending aorta. The blood from the inferior vena cava enters the right auricle, passes through the foramen ovale into the left auricle, then into the left ventricle which pumps it into the ascending aorta (Fig. 3). The following explanation of the circulation of this instance of closure of the aortic orifice is offered, which explains at least a possible circulation.

8. Williams: *Obstetrics*, New York, 1912, p. 156.

Blood from the superior vena cava followed the same course as in the normal fetal circulation. Blood from the inferior vena cava entered the right auricle, passed through the foramen ovale and entered in whole or part the left ventricle where it was forced back through the

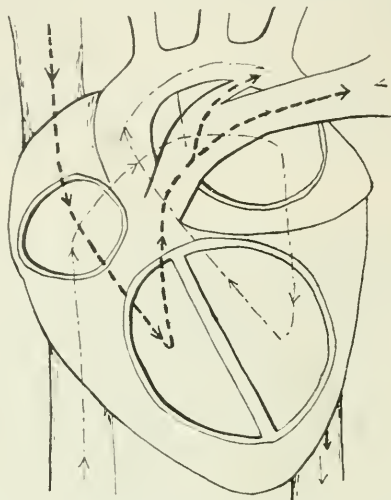


Fig. 3.—Diagram of normal fetal circulation (after Spalteholz).

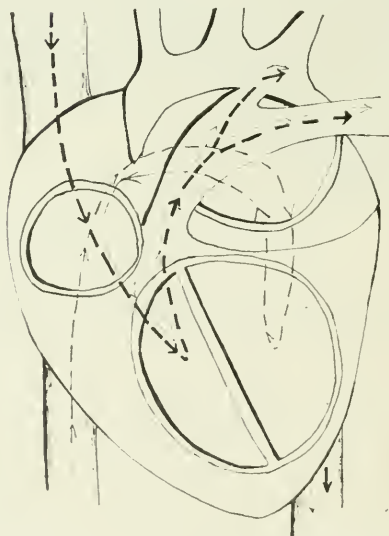


Fig. 4.—Diagram of circulation with obliterated aorta.

foramen ovale into the right auricle, where it went with the blood from the superior vena cava into the right ventricle, then into the pulmonary artery, where it divided, part going into the pulmonary circulation and the remainder into the aorta through the ductus arte-

riosus. Blood returning from the pulmonary circulation into the left auricle was forced by contractions of the left ventricle through the foramen ovale into the right auricle, where it mixed with the other blood (Fig. 4). Such a circulation could be successfully continued as long as the right ventricle was able to maintain the systemic as well as the pulmonary circulation, with death occurring when the right ventricle failed.

I wish to thank Drs. E. G. Kirk and H. Gideon Wells for their assistance.

THE USE OF CREAM AND PRECIPITATED CASEIN IN INDIGESTION WITH FERMENTATION *

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A few months ago I had the opportunity of studying a very interesting feeding case in the outpatient department of the Children's Hospital. The subsequent feeding history deserves special attention.

Baby D., birth weight 8 pounds, nursed one week, was then put on various formulas of milk, water, and lime water, and sometimes Mellin's food. All the formulas were of fair proportions. She came to us on June 21, 1915, at the age of 10 weeks, weighing 7 pounds 1 ounce, with a history of projectile vomiting, hunger, and markedly excoriated buttocks. The sample stool that day was hard and yellow. She was given a trial laboratory formula of 1 fat, 4.5 lactose, 1.5 protein, limewater 50 per cent. of the milk and cream.

The accompanying table shows the date of each visit, the weight, the number of stools a day, and the formula ordered at that date. The plus signs in the column showing the number of stools indicate a diarrhea with no definite number mentioned.

Explosive vomiting followed the taking of the trial formula, and the baby passed a great deal of gas. The case was considered one of indigestion of fats, and the baby was put on a formula containing no fat, which furnished 57 calories per kilogram, and the food was boiled.

This formula did not agree any better than the previous one. The mother of her own accord gave a mixture of condensed milk and water. The baby gained 25 ounces in forty-one days on it. For the first few days it did not vomit, but then it began again as badly as ever. Everything on the whole went fairly well until four days before the next visit, when a diarrhea started, with many loose, green, slimy stools, containing streaks of blood. The case looked like an infectious diarrhea, but there was no rise of temperature. The stool was planted for gas bacillus, and the baby was given a 3 per cent. barley water, with 2 per cent. lactose.

It took the mixture well and vomited but little, yet the number and character of the stools remained the same. The gas test on the stool was positive. This test was done twice later and found negative each time. No change was made in the food. On August 7 milk of bismuth was given in 0.5 dram doses after each bowel movement.

In two more days, on the 9th, the mother reported vomiting, from ten to twelve watery stools without blood or pus, and that the baby was in rather poor condition. The buttocks were still excoriated. The "formulas" from this time to the end of August were fat free, or with small amounts of fat, contained 4 per cent. or less of total lactose, a high protein, and some lime water. The stools often showed a marked excess of soaps even on the skimmed milk.

On September 1 Dr. Sylvester, head of our outpatient clinic, was consulted, and we concluded that the lactose was responsible for the vomiting, diarrhea and excoriations, which were on that day more marked than ever.

I ordered a laboratory formula in which precipitated casein was substituted for the protein in the skimmed milk. The percentage of lactose in precipitated

* Submitted for publication April 27, 1916.

* From the outpatient department of the Children's Hospital.

* Read before the New England Pediatric Society, January, 1916.

casein is about 0.1, according to a chemist's analysis. In putting 2 per cent. precipitated casein into a formula, only 0.002 per cent. lactose would be added thereby. The cream adds about 0.12 per cent. to each 0.75 per cent. fat, as a 32 per cent. cream is always used by the laboratories. Thus, in a mixture containing 0.75 per cent. fat and 2.5 per cent. precipitated casein, there would be present about 0.13 per cent. lactose. On September 1 the baby was given a formula representing 0.75 per cent. fat, 0.12 per cent. lactose, 2.5 per cent. precipitated casein, with a little lime water. A little paregoric was given.

OUTLINE OF FEEDING HISTORY OF BABY D., THE QUANTITIES IN THE
FORMULAS INDICATING PERCENTAGES

Date	Weight, Lb. Oz.	Stools*	Fat	Lac- tose	Dextri- Mal- tose	Mal- tose	Skim- med Milk Protein	Precip. Casein	Lime Water†	Barley Starch	Ounces Daily
6/21	7 1	..	1	4.5	1.5	50	24
6/25	7 ..	2	0	4.5	1.2	50	0.5	..
8/ 4	8 9	+	2	3	32
8/ 7	8 3	+
8/ 9	7 14	11	0	2.75	2	40	48
8/10	8 6	8
8/13	8 9	10	0	2.5	2.1	40
8/16	8 6	5	0	3	2.5	30
8/18	8 5	4	0.25	4	2.5	30
8/23	8 5	8	0.25	3.5	2.5	10
8/25	8 5	+	0.5	3.58	2.5	40
8/27	8 6	11
8/28	8 8	10
8/30	8 4	+
9/ 1	8 4	+	0.75	0.12	2.5	40
9/ 3	8 4	7
9/ 7	8 6	8
9/10	8 5	2	1	0.15	2.5	40
9/13	8 8	3	1.5	0.22	2.5	40
9/16	8 8	3	2	0.29	2.5	40
9/21	9 ..	4	2.5	0.36	2.5	40	64
9/29	9 8
10/ 7	10 4	..	2.5	0.36	0.25	2.5	40
10/18	11 2	4	2.5	0.35	2	2	40
10/25	11 5	5	2.5	1.05	4 *	0.5	1.5	40
11/ 3	11 8	3	2.5	1.05	5.5	0.5	1	40
11/17	11 14	2	2.5	1.4	5.5	0.75	0.75	30	0.50	..
11/29	11 11	9	2.5	1.9	5	0.5	1.10	20	0.75	..
12/17	12 6	2

* Plus signs indicate diarrhea, number of stools not mentioned.

† Percentage of milk and cream.

In two days, the mother thought the baby acted much better. It slept better and had less gas, but there were from six to seven stools a day, showing no change from the high protein variety.

On October 7 the baby weighed 10 pounds, 4 ounces; she was happy and slept well for the first time in her life. She had good stools, with no excess of soaps, and showed no excoriations. It was then five weeks since the institution of the low carbohydrate formula, and it was thought that the digestive tract had had a sufficient rest from lactose, the only sugar that could have caused trouble, as it was the only variety the baby had had in two months. I preferred to try a malt sugar first to test out the carbohydrate tolerance.

On October 25 it was reported that the child was very hungry, cried much and vomited a great deal. We discovered that on account of the baby's hunger the mother often gave 16 ounces at a time. We laid the vomiting to this error, and advised the mother accordingly.

The baby was doing very well, and it was considered that a little lactose now would do no harm. So I decided to add a little in skimmed milk and watch results. At the same time I increased the dextrimaltose to 4 per cent. The lactose in this mixture amounted to 1.05 per cent.

During November the buttocks were again slightly excoriated. On November 29 the baby lost 3 ounces and was constipated. It would not eat or sleep, and no underlying cause was found, although it was not thought to be an indigestion. A little malt sugar was put into the formula to help the constipation, the precipitated casein was left out, and all the protein added in the form of skimmed milk protein.

On December 17 everything was satisfactory to the mother, and she had given of her own accord orange juice, farina, bread and crackers with no ill results, although the baby was only 8½ months old.

This case seems to have been one of lactose intolerance. The baby gained and did exceedingly well when the lactose was greatly reduced beyond the means ordinarily used in treating a case of indigestion with fermentation. The dextrimaltose did no harm, even when added to 5.5 per cent. Starch did no harm either as a diluent or in the form of bread and crackers. The lactose in the final mixture amounted to 1.9 per cent. I never tried adding any extra lactose. It is interesting to note that the excoriations continued at one period while the stools were of the high protein variety and alkaline.

Having had success with this rather obstinate case, I attempted to treat other cases of indigestion with fermentation in this same manner. I shall report these very briefly.

Baby H. came to us on October 13 weighing 8 pounds at 6 months, with an illness of from ten to twelve stools a day and excoriations. The baby was immediately started on a very low lactose formula, similar to that described in the Baby D. case, and in five days the excoriations were gone and the baby was constipated. In the first nine days it gained 13 ounces. Dextrimaltose was gradually added and skimmed milk protein gradually substituted for the precipitated casein, so that in six weeks the baby was on a mixture of 2.5 per cent. fat, 6 per cent. dextrimaltose, 1.25 per cent. protein, 0.75 per cent. barley starch, and the child had gained 3 pounds, an average of 8 ounces a week.

Baby G. on October 4 gave a history of frequent, loose and frothy stools. It was put on the low lactose mixture, and in the first week gained 6 ounces and was having four normal stools a day. The excoriated buttocks had cleared in three days.

Baby T. was started on September 20 on fat-free buttermilk. The child was having from twelve to twenty-four stools a day and had excoriated buttocks. After four days the condition was not improved. The baby was then started on a low lactose formula. In three days the stools numbered three a day, and in two more days the buttocks were perfectly clear. After ten days the formula was worked up from 0.5 to 2.5 per cent. fat. I was about to begin to add dextrimaltose when, in my absence, the formula was changed to 2 per cent. olive oil, 4 per cent. dextrimaltose, 1.4 per cent. protein, 0.75 per cent. barley starch. Three days later the mother reported vomiting four times a day, and twelve or more stools a day. I put the baby back on a low lactose formula, but the mother never returned for further treatment.

Baby McC. had a similar history of loose movements and excoriations. In eleven days of treatment the stools were reduced to two a day, and the excoriations were soon gone. The baby gained 17 ounces in the eleven days. Constipation occurred while building up the dextrimaltose, and was still present after two and one-half months of treatment. The baby gained $2\frac{1}{2}$ pounds in the two and one-half months. It was taken off the precipitated casein after four weeks of treatment.

Baby F. came down from ten stools to one stool a day in one week, and gained 8 ounces during the seven days.

Baby T. McC. cleared up from a similar condition in three days. He was treated for five weeks, when finally taken entirely off the precipitated casein, and gained $1\frac{3}{4}$ pounds. After the third day he did not have over three stools a day.

Baby W. had loose, green, watery stools with mucus, pus and blood, which gave negative tests for the gas bacillus. Lactose solution did not help, and the child lost 18 ounces in five days. It was then put on the low lactose formula, and in nine days the stools were normal, and the baby gained 13 ounces. In four weeks more the baby was off the precipitated casein, and had gained 2 pounds 9 ounces in the four weeks.

Baby C. had three formed stools a day while being treated in the outpatient department. The buttocks, however, were excoriated. He was put on the low lactose formula, and the excoriations healed up permanently, the formula not being used after two weeks of rest from the lactose.

Baby F. had a similar history, the buttocks clearing up immediately.

Baby C. was having from fifteen to twenty stools a day with excoriated buttocks. He became constipated and the buttocks were clear in three days, neither symptom again returning. He was kept on the low lactose formula for seven days, not receiving precipitated casein after that.

Baby W. had excoriated buttocks while being fed in the outpatient department. I gave him the low lactose formula, and at the next visit in six days the excoriations were all gone. Another attendant put him back on a moderately high lactose formula, and the baby soon became excoriated. He probably did not have a long enough rest from the carbohydrates.

Baby S. developed loose stools and excoriated buttocks while being treated in the outpatient department. She was put on the low lactose formula, and became constipated in four days. The excoriations were gone.

Baby S. cleared up from loose stools and excoriated buttocks in twelve days, having gained 4 ounces during the time.

Baby S. had a diarrhea for two days from too much Mellin's food. He was not excoriated. He was put on the low lactose formula and became constipated immediately.

I have cited here fifteen babies that did well. Eight others were treated with this formula, three not coming back for further advice. In two of the other five the treatment was interrupted in one by pneumonia, in the other by accidental poisoning with arsenic. In one

case the mother became discouraged because of the outpatient routine. She desired to have the baby treated immediately. The baby was not very sick and I learned later from the social service nurse that it was gaining slowly on milk and water.

In another case we were forced to give cane sugar because the baby absolutely refused food without it. This caused delayed recovery, but after two months the child was well and had gained $1\frac{1}{4}$ pounds. It had more excoriations than any baby I have ever seen. These cleared in two weeks. The last patient in my list did not improve, and the mother admitted she had been giving other milk because the child was hungry.

I recently looked over about 100 cases of indigestion with fermentation from the outpatient department records of the last fifteen months previous to my series. I found that almost invariably the treatment had been a formula containing from 2 to 4 per cent. lactose with no other sugar added. In some cases, buttermilk was given because a positive test for gas bacillus was found.

It was very difficult to obtain in figures the exact number of days necessary to clear the diarrhea and excoriations in each case of this earlier series. Very often the condition of the bowels or the buttocks was omitted from the record. Many times the patient was absent for two months or more after treatment, and no mention was made of the old condition in the new note.

On the whole, the cases of indigestion with fermentation, when the treatment consisted of from 2 to 4 per cent. lactose, were much longer drawn out than when the treatment was by the very low lactose formula. A point to guard against is the possible loss of weight during the first two or three days because of the low caloric content of the formula. Very often the baby will refuse the food at first, because it contains nothing sweet. The mother should be warned about these two possibilities from the start, and should be encouraged by the rapid clearing of the buttocks and diarrhea. In only three cases was the mother's confidence apparently lost.

Another difficulty in using the cream and precipitated casein mixture is its preparation. The higher the percentage of cream used, the lower will be the lactose content of the formula. As for making precipitated casein in the home, it is almost out of the question. There are on the market preparations of powdered precipitated casein which dissolve readily in hot water, and leave too slight a sediment or curd to block up the hole in the nipple. The precipitated casein made from skimmed milk and not dried and powdered is of course insoluble, and remains in curd form at all temperatures. This blocks the hole in the nipple and requires a great deal of trouble at each feeding. Even

putting the curd through the homogenizing machine does not relieve the difficulty, although it makes the curd finer.

If a 32 per cent. cream is obtainable, the powdered casein may be purchased at a low cost, and the formula prepared at home. In Boston the mixture is readily prepared on order by either the Walker-Gordon or Hood laboratories.

On the average it should take from two to four weeks to carry a child to a point at which the carbohydrate is again raised to 5 or 6 per cent., and the precipitated casein omitted from the mixture. As an increase in the protein from skimmed milk necessitates the addition of lactose, the protein should be kept low for a long time, from 1 to 1.25 per cent.

Nothing is claimed for the precipitated casein in this method of feeding except that it makes possible a very low carbohydrate food, it being almost lactose free. Whether the reduction of the soluble salts brought about by its use is of any benefit I am not able to say. I do not think the precipitated casein helps because of the preponderance of protein fermentation that it affords over that of carbohydrate, because this balance is soon reversed when the fat and dextrimaltose are raised, with no return of the symptoms. In the case of Baby D. the protein fermentation exceeded the carbohydrate fermentation, as the stools were alkaline, but the excoriations and loose movements continued.

There are many cases of indigestion with fermentation brought about by an excess of cane sugar or malt sugar. These are relieved by dispensing with the disturbing sugar. It is my opinion that the symptoms would clear up faster and surer if all the carbohydrates were reduced to a minimum for a while, and then a different one gradually substituted for the one that caused the disturbance.

In treating fat intolerance we try at first to give a food free from fat, and gradually build up a tolerance. It seems, therefore, reasonable in treating carbohydrate indigestion to get the carbohydrate as low as possible for a while, and gradually build up a tolerance.

It is interesting to note in my series how well each baby took fat up to 2 per cent., 2.5 per cent., and even 3 per cent., while on the low lactose formulas. This method may be a help in establishing a fat tolerance in some cases.

Of what use such a formula may be in the noninfectious diarrheas of the summer months I am not able to say. As most methods so far have led to some discouragement, perhaps this one may prove valuable.

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SUGGESTION AS A THERAPEUTIC MEASURE IN NOCTURNAL ENURESIS *

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Failure to control the bodily functions of excretion constitutes a breach of conduct so offensive to civilized society that its origin as a social refinement is apt to be obscured. Although it is "only necessary to scratch civilization to find savagery," there is a tendency to forget the influence of traditional associations on civilized activities.¹ Primitive impulses, the utility reactions of a simple environment, still survive. Their readjusted nervous mechanisms are generally less stable than the reflexes of instincts subject to less direct social scrutiny. All the newer requirements of civilization call on the organism to develop self-control. Consequently many customary actions of frequent repetition speedily become unconscious mechanisms. Hand in hand with this automatic activity goes an increase in the emotional value of its omission, still more of the performance of such activities contrary to custom.² In the mature individual lapses in control of the urinary bladder suggest at once a psychopathic taint, for even positive, somatic disorder rarely imposes loss of control beyond the power of voluntary modification. Although nocturnal enuresis during the first two years of life is considered physiologic, training in regular habits during the first year may accomplish much. If by the end of the third year restraint has not become habitual the situation should be looked on as one demanding more than mere nursery attention. Few cases of uncomplicated enuresis diurna are seen in children of ordinary intelligence, but sleep presents conditions to which certain of these ill-balanced children are unable to become adjusted. As a result various neurotic manifestations develop, sleep walking, night terrors, bed-wetting, all rightly regarded as evidence of nervous instability. The annoyance that a child disposed to bed-wetting causes itself and its attendants is so much greater than that resulting from other neurotic symptoms that its frequency is naturally overemphasized. Even among nervous children its characterization as one of the commonest diseases of childhood³ is not substantiated by experience. Among 800 nervous children of various

* Submitted for publication June 6, 1916.

1. Boaz, F.: *The Mind of Primitive Man*, Journal of American Folklore, 1901.

2. Baldwin, J.: *Social and Ethical Interpretations*, New York, 1902.

3. Mello-Leitao: *Treatment of Nocturnal Enuresis in Children*, Brit. Jour. Child. Dis., 1912.

nationalities admitted to Phipps Psychiatric Dispensary, ranging in age from 5 to 16 years, only 7 per cent. were bed-wetters. Various theories point to its obscure causation, this suspicion being intensified by an analysis of the cases. Admitting the occurrence of a purely objective type, due to congenital defects, intestinal parasites, diabetes, cystitis and other organic disturbances, there is another group of subjective cases of an entirely different character. In these children evidence of psychic inferiority may be easily elicited or it may be quite elusive. Consequently they are often dismissed as habitually nervous, their malady to be outgrown. Successful treatment of these patients with empirical remedies is frequently as surprising as it is inexplicable. The element of mystery thus added temporarily enhances the virtue of the cure until its failure for each and every case relegates it to the limbo of the charlatan, another nostrum taking its place.

Without attempting thoroughly to analyze a situation presenting many physiologic elements of controversy, a brief recapitulation of the definite, biologic manifestations bearing on the cases here clinically reported is offered for criticism. The earliest response of the human organism to bladder stimulation is an involuntary process. During the first few months of life it represents the activity of a purely unconditional,⁴ spinal reflex, the mechanism of which resides in the sacral and thoracic autonomic systems.⁵ Awake or sleeping the normal infant exerts no attempt at voluntary control. Even after he is able to associate a manifest degree of discomfort with his unpleasant habit he is unable to readjust himself to the situation without assistance. Whether the muscular structures at the neck of the bladder are stimulated by chemical or physical agents the subsequent reflex activity seems to be touched off by the stimulus of the few drops of water in the posterior urethra.⁵ The primitive nature of the mechanism is shown in the fact that section of the thoracic-autonomic innervation does not affect the reflex, though it is abolished when the pelvic nerves are cut.⁶ This difference in function as well as in later dissociation phenomena might be explained on the ground that the two systems have an independent, biologic history of dissimilar chronology.⁷ Thus, early reflex activity, controlled wholly by instinct, independent of cortical association, reveals the regularity of primitive organic response to environment, through the nervous system. Moreover, one may recognize herein another function of nervous tissue, that of forming new reflexes in

4. I have called these reflexes of recent formation "conditional reflexes," in order to distinguish them from the ordinary reflexes to which I have given the name "unconditional reflexes."—*Pawlow*.

5. Luciani, L.: *Human Physiology*, Translation, London, 1913, ii.

6. Elliott, T.: *The Innervation of the Bladder and Urethra*, *Jour. Physiol.*, 1907.

7. Langley, J.: *The Autonomic Nervous System*, *Brain*, 1903.

order to adapt the organism to its social environment. These reflexes of recent formation, or conditional reflexes, together with the cortical, association neurons or analyzers, are responsible for all higher, nervous activities. They represent the reaction of the organism as a unit in response to a localized stimulus. They are phenomena of a higher, more complex order than are simple contractions or other direct changes in the motor organs at the point of stimulation. Pawlow's experiments on animals indicate that fully formed, conditional reflexes exhibit great sensitivity to all sorts of conditions, on which account they are subject, in circumstances of everyday life, to continued variation, often to complete inhibition.⁸ Krasnagorski's⁹ observations show the same results in children. Three distinct types of inhibition have been recognized: one conditioned by drowsiness and sleep; another due to the synchronous arrival, at the higher centers, of extrinsic and intrinsic stimuli giving rise to other reflexes; a third due to disharmonies between conditional and unconditional stimuli from which the reflex was formed. Returning now to events in the life of the unconditional or primitive spinal reflex concerned with urination, one finds that the educational procedure adopted by the attendant induces voluntary control in the child by presenting frequently a temporary association stimulus coincident with the biologic stimulus. The child attends to the nursery chair or other associative object at the same time that the desire stimulus is about to react. Through this cooperation he is enabled gradually to build up a definite control, stimulated by the visual or auditory image associated with the accomplishment of desire. These temporary stimuli or associations, presented repeatedly in conjunction with the unconditional stimulus inducing desire to empty the bladder, make for themselves new inhibitory paths. Impulses which formerly went to a particular region of the nervous system now become directed to a different one, thereby inducing controlled action in the nature of a conditional reflex. Thus the child, at first forced to conform to rules of conduct, acquires a habit thereafter voluntarily cultivated. This is all the more easily directed or diverted since "the bladder is very sensitive to reflex stimulation, every psychical act and every sensory stimulus being apt to cause contraction or increased tone in its wall."¹⁰ The new reflex formed has a different afferent neuron, "the voluntary act of urination being essentially a reflex through the central nervous system."

8. Pawlow, I.: *The Investigation of the Higher Nervous Functions*, Brit. Med. Jour., 1913.

9. Krasnagorski, N.: *Ueber die Bedingungsreflexe im Kindesalter*, Jahrb. f. Kinderh., 1909.

10. Howell, W.: *Textbook of Physiology*, Philadelphia, 1915.

Elliott has observed that the pelvic nerves cause the bladder to contract. They also inhibit the sphincter, hence they are the nerves of micturition. They affect the primitive visceral movements that are the first need of the animal, to wit, the voidance of the excreta. It seems to be a reasonable assumption that they are the aboriginal nerves. The hypogastrics represent later refinements, whereby these acts may be deferred to a moment better suited to the other activities of the whole animal. They are the nerves which facilitate retention of urine and justify the belief that this second condition of the muscle has been recently developed.

This act consciously acquired and assiduously practiced is gradually relegated from a wholly conscious to a largely unconscious performance. In the infant, whose associative mechanism is undeveloped, no voluntary control is possible until there is a linking up of the vegetative and associative nervous system. After the age of 2 years the unconditional mechanism is firmly established in the normal child as a conditional reflex. The association between motor activity and its emotional response thus occurs more or less faultlessly in the absence of conscious supervision. The success of the process depends, of course, first, on an ability consciously to attend to the stimulus—sensation, desire—which underlies the motor impulse, together with an ability to interpret these sensations of behavior in terms of conduct; second, an ability unconsciously to interpret these phenomena. For “eager desire one must substitute attention,”¹¹ a condition which can be realized only in individuals possessing a fairly well-balanced mentation. Thus, children who show a marked disagreement in mental and chronologic age are unsatisfactory subjects. Those who respond most readily to constructive treatment are intelligent though ill-balanced individuals. Again, success in education depends on the anatomic continuity of the newly formed reflex arc, this in turn depending on the permanency of the synapses. Disjunction most readily occurs in newly formed association centers, the autonomic system being especially vulnerable from the fact that no efferent fibers of the system run from the central nervous system to the bladder without having a nerve cell in their course.¹² Thus fatigue, to which conditional reflexes are sensitive, or the vagaries of the ductless glands, with whose functioning the autonomic system is intimately associated, may readily induce synaptic disjunction. In case of this lack of associative activity the primitive condition easily dominates the situation, thus abolishing voluntary control. Elliott's observation that epinephrin, however applied to the bladder never causes any effect other than that of relaxation may thus

11. Pawlow, I.: *The Work of the Digestive Glands*, London, 1910.

12. Langley, J.: *Nerve Fibers of the Bladder*, *Jour. Physiol.*, 1911.

explain the theory of Konrádi,¹³ Williams¹⁴ and others that the underlying cause of nocturnal enuresis is always a glandular disharmony. The favorable action of atropin on many of these cases¹⁵ may also be accounted for in its sedative affinity for the autonomic fibers. Applying Pawlow's observations on inhibition to the reflex in question, we may make a logical explanation of the hypothesis of Fürstenheim,¹⁶ Collin¹⁷ and others who regard "the soundness of sleep as the initial factor," or with Herrman's¹⁸ classification of bed-wetting with tics and speech defects, or with Pronstein¹⁹ whose examinations reveal constant anatomic lesions.

In this group of ill-balanced children, whose unstable nervous mechanism is indicated by the tendency to bed-wetting, one is confronted with a problem of biologic adjustment. Success depends on the ability to change a situation which, during sleep, simulates a primitive state controlled by an unconditional, reflex mechanism. Granted favorable circumstances, all that is required for a positive effect is the ability to awaken attention, thereby establishing associative control through a conditional reflex. By presenting repeatedly a definite stimulus the bladder is reeducated in a proper method of functioning. The form in which this associative suggestion should be presented depends on the point of view of the observer. It certainly does not present a new or unique method of procedure, for it is narrated in the Saxon Chronicle that the Magi also taught the patient suffering from this disorder to drink the ashes of a pig's pizzle in sweet wine, and so to make water into a dog's kennel, adding the words: "lest I like a hound, should make urine in my own bed."²⁰ Bruni²¹ reported "twenty-three cases treated by injection of normal salt solution into the arachnoid sack, with lumbar puncture, seven of which were cured." Allaria²² reported "pseudo-epidural injections of normal salt solution under the skin, merely, with the same success as when injected into the

13. Konrádi, D.: Die Organotherapie der Enuresis nocturna, Pest. med.-chir. Presse, 1910.

14. Williams, L.: Adenoids and Nocturnal Enuresis, Brit. Jour. Child. Dis., 1909.

15. Simpson, J.: Incontinence of Urine in Children, Edinburgh Med. Jour., 1913.

16. Fürstenheim: Enuresis nocturna infantum, Therap. Monatsh., 1908.

17. Collin, A.: Contribution à l'étude de l'énurésie dite essentielle, Gaz. d. hôp., 1911.

18. Herrman, C.: The Treatment of Enuresis by Reeducation, Arch. Pediat., 1910.

19. Pronstein, R.: Russk. Vrach., 1914.

20. Cockayne, O.: Leechdoms, Wortcunning and Starcraft, London, 1864.

21. Bruni, C.: Il metodo Cathelin nella cura dell' incontinenza essenziale d'orina, Atti d. r. Accad. Med.-Chir., di Napoli, 1905.

22. Allaria, G.: La punctura pseudo-epidurale nell'enuresi essenziale dei bambini, Pediatria, Napoli, 1912.

sacral canal." Rotch,²³ following an old precedent, advocated "raising the foot of the bed so that the urine shall not irritate the neck of the bladder." Various clinicians, resorting to placebos of bitter decoctions, by instructing the child as to administration and results, report cures more or less permanent. Punishment sometimes works wonders. In spite of a degree of success, these methods, all of which are frankly modifications of suggestion, are open to criticism. One is justified in shrinking from surgical procedures if equally satisfactory results may be attained through less objective methods. Again, in spite of the harmlessness of a placebo, the possibility of drug habits, especially in children of neuropathic constitution, is to be considered in choosing a therapeutic method.

As a harmless, and, in the experience of the writer, a uniformly efficient means of treatment, the following technic in applying suggestion to these cases is presented. A set of four associative sentences is printed on a card. The wording is not immaterial, though it may be varied to suit the case. It should be positive and of simple structure. Following are the stimulus words used for the cases here reported:

- I am not going to wet the bed.
- I am going to wake up at midnight.
- I shall get up and pass water.
- I shall not wet the bed any more.

This is to be repeated ten times, twice a day, preferably during the act of urination, and at bedtime just before going to sleep. The card is then put under the child's pillow. This method, combined with no other measure, was employed in treating the ten patients whose cases are reported below. Auditory-motor stimuli were at first used, with satisfactory results in high-grade children, but were less applicable to children of moderate responsibility. The visual-motor method has been adopted, however, as a better routine procedure. The subjects were all schoolchildren who, from their appearance and conduct, were tacitly neurotic. Treatment was begun Feb. 1, 1916, and is being continued. The results here reported are therefore of four months' duration. The two girl subjects were at home while all the boy subjects were inmates of the Baltimore Parental School, an ideal institution of its nature. Each subject had a thorough physical and mental examination in order to rule out etiologic factors other than those of psychic inferiority. The urine was examined in each case and was within the range of normality respecting quality and quantity. The majority had been under unsuccessful medical treatment.

Various historical factors are shown in the table of clinical data and the results are there briefly indicated. In general, one may say

23. Rotch, T.: *Pediatrics*, Ed. 5. Philadelphia, 1906.

CLINICAL DATA OF TEN PATIENTS TREATED FOR NOCTURNAL ENURESIS

Name	Sex	Chronological Age	Binet-Simon Age	Nocturnal Enuresis	Remarks	Results
H. N.	M	12	9	From birth, nearly every night	An ill-balanced truant; neurotic family history; cooperative, eager to stop "floating"	Perfect for 2 months; left school and lost sight of; wakes up himself
E. T.	M	12	12	From birth, nearly every night	An ill-nourished, intelligent, cooperative truant; poor home environment; psychopathic family history	Twice in February, not since; wakes up himself
O. H.	M	14	14	From birth, 2 or 3 times weekly, till 8 years, when truancy began; every night since	Highly emotional, somnambulist, snake dreams and terrors; family history of drink and debauchery	Three times only; wakes up himself
R. S.	M	11	11	From admission to Parental School 6 months before; every night; before occasionally	Bright boy, no other neurotic traits; family history good; truancy, from bad neighborhood	Twice only; wakes up himself
L. K.	M	14	8	From infancy every night	Dull boy; family history not known	Improved, but still about once a week; has to be awakened sometimes
C. P.	M	12	8	From infancy every night	Fairly bright boy; family history not known	Once in each month for 2 months; paroled and lost sight of
R. W.	M	12	12	Twice weekly from birth; every night since admission to Parental School, 6 months before	Bright boy; family history good	Only once since beginning; wakes up himself
W. W.	M	13	13	Occasionally all his life	Bright boy; poor environment	Once only from beginning
B. E.	F	9	9	Father drinks, somnambulist, bed-wetter; mother "fits and spells"; home environment "the worst"	Nocturnal and diurnal enuresis began after diphtheria at 5 years; every night; night terrors; a brother has same habits	Much improved; one month perfect; later "forgot" and wet bed once or twice a week
H. B.	F	12	12	Family history good; mother rheumatic	Nocturnal enuresis since scarlet fever at 5 years; nearly every night; night terrors; large, over-developed; infantile; type, normal sella turcica; choreiform movements	On second night of trial wet bed; not once since; wakes up herself.

The eight boys were observed at the Baltimore Parental School. They were all white, and were all committed for truancy.

that the mass result was entirely positive. This is evident when it is recalled that all these subjects were chronic bed-wetters, the act occurring, in the majority of cases, every night. Under treatment cessation of the habit was essentially complete in all but one case, L. K., whose mental level explains his irresponsibility and poor success. As Dubois long ago suggested, "enuresis may be cured by education only, interrupting the child's sleep for this purpose in the middle of the night. It is thus that good habits are created." It is of interest, however, to note the result of this dictum on one of these subjects, H. B. For several weeks the girl was nightly aroused from sleep by her mother and urged to micturate; rarely would she awaken so thoroughly as to recall the incident the following day. The result was negative, bed-wetting generally occurring as before, but later in the night. This well illustrates the part played by consciousness in a successful reaction. The child must assume the responsibility of waking up and caring for himself.

SUMMARY

From this point of view uncomplicated nocturnal enuresis is an element in the psychic regression of an unstable organism toward a more primitive biologic state.

The mechanism concerned in inhibition is an unconditional reflex which through social evolution becomes a conditional reflex.

The object of treatment is to assist normal development in the associative mechanism, tending thus to induce a conditional reflex.

The means employed are the presentation of a series of associative visual stimuli.

Ten clinical cases are presented.

PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE OF RESPIRATORY DISEASES OF THE PAST YEAR

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RESPIRATORY DISEASES, MORTALITY AND MORBIDITY

Woodward¹ has made a study of the respiratory diseases as a factor in the causes of infant mortality. In 1913 in the first year of life the diseases of the respiratory system ranked third in the causes of death; 15.85 per cent. of the total deaths were due to respiratory diseases; 25 per cent. of the mortality from respiratory diseases at all ages occurred in the first year of life. Bronchitis and pneumonia caused 96 per cent. of the deaths by respiratory diseases in infants. The mortality in cities was slightly higher than in the country. The third week of life was the maximum danger period for bronchitis and pneumonia. He concludes that prevention of death in infancy from respiratory diseases is a task which requires the united efforts of the prenatal nurse, obstetrician, midwife, pediatrician and infant welfare station.

Haynes² believes that vital statistics do not measure the importance of respiratory diseases, since most patients recover, but a vast amount of damage is done which is not shown by the death rate. The ordinary infectious cold results in ear, kidney and cardiac damage of no small amount. From November to June the bulk of pediatric practice is due to respiratory diseases. Forty per cent. of the deaths in the first five years are due to respiratory conditions and 25 per cent. of all deaths from respiratory diseases are in the first five years. Rickets, infectious diseases, enlarged adenoids and tonsils all predispose greatly to respiratory infection. There are certain anatomic factors in the young which render any respiratory inflammation serious; that is, the narrowness of the respiratory passages, nose, larynx, bronchi, which are easily obstructed by the secretions, the shape of the thorax, the soft ribs, and the habitually recumbent position. Lowering of resistance by cold, fatigue, autointoxication or poisoning by food or chemical substances are also important predisposing factors. The actual infection usually takes place by spray from the mouth and nose discharges of an infected person. The helpless infant must be protected from dust, both outdoors

1. Woodward, W. C.: *Am. Jour. Obstet.*, 1916, lxxiii, 362.

2. Haynes, R. S.: *Arch Pediat.*, 1916, xxxiii, 81.

and indoors, from smoke which is harmful as a mechanical irritant, and from crowding, since close contact increases the possible transmission of infection by sneezing and coughing.

In the regulation of infectious diseases, early quarantine is more important than disinfection and fumigation afterward. Crowding is especially dangerous in hospitals, and the box system, or screens, is a great aid in preventing transmission of infection. The early exclusion from school of every child with a slight cold is absolutely necessary to prevent transmission of colds, not only to his schoolmates, but to the smaller children in their various families. The discharges from the nose and mouth of a sick child should be carefully caught on gauze which should be burned, and the bedding, etc., disinfected.

Among preventive measures are careful feeding, enough sleep, proper clothing, a clean skin and careful regulation of the bowels. The air in the house should be kept at 65 F., with a humidity of 60 per cent. Young children should not be taken out on windy and damp days.

Hill³ states that epidemics of colds are most common when the humidity is great, the temperature variable but cold, in raw weather with thawing snow or cold rain and wet ground. Persons living in the open air are free from colds. Children during their holiday paddle all day in the sea with bare legs. When they are shut in the schoolroom, colds begin. This is probably due to propinquity, since children are nearer together indoors. Out of doors the sprays of saliva and nasal mucus are blown away and are less likely to come in contact with healthy children. The colds may be caused by bacterial infections, dust, irritating fumes, pollens, etc. Hill has made observations on the nasal mucous membrane and has found that out of doors it is pale, taut, and does not pit on pressure with a probe. Indoors it is swollen, congested, covered with thick secretion and pits on pressure. He thinks this is due to the fact that outdoors the air nearer the ground is warmer because it moves less rapidly than at the level of the head. Indoors the reverse is true. The floors are cold and drafty and the head is immersed in hot, stagnant air. He believes that the nasal obstruction is due to chilling of the feet when the head is warm, and has found that warming the feet will relieve the congestion observed indoors.

Ideal conditions would give a warm floor, radiant heat and abundant cool air in motion. Open fires approach this more nearly than any other method of heating, since the feet can be warmed by radiant heat and most of the heat goes up the chimney. He believes that the boggy condition of the nasal mucous membrane predisposes to infection by bacteria. Sudden changes from the warm indoor air to the colder air

3. Hill, L.: *Brit. Med. Jour.*, 1916, i, 541.

out of doors are bad on account of the sudden demand for more blood in the nose which is necessary to compensate for the cooling of the mucous membrane and the more rapid evaporation from its surface.

Peiper⁴ believes that respiratory infections in infants come not from chilling alone, but from infection from other persons. Infections are not always influenzal, though "conveniently classed as grippe." Infants should be carefully protected from these infections, as far as possible, by a room of even temperature, avoidance of chilling, and of cold drafts, especially at the bath. In raw weather a child should remain indoors. The mother should avoid infected persons and if she contracts cold or cough, must use every effort possible to protect the child from infection.

Peiper describes accurately and briefly the various infections of the upper respiratory tract, the bronchi and lungs. He also describes the treatment of the various conditions arising more fully and carefully than is usual with most foreign writers. The treatment of capillary bronchitis and bronchopneumonia are especially good. The technic of, and indications for, cold packs, mustard packs, hot baths, etc., are given in detail in excellent manner.

Miller and Noble⁵ investigated the effect of chilling on the incidence of respiratory diseases in rabbits. They used rabbits infected with the *Bacillus botrysepticus*, because it is an organism normally pathologic for rabbits. They conclude that respiratory infections of rabbits are favored by chilling the animals after they have been accustomed to heat, and that the weight of evidence does not justify the elimination of cold as a possible though secondary factor in the incidence of respiratory diseases.

Marked changes of temperature from low to high predispose even more to respiratory infection than from high to low.

ROENTGEN RAY IN DIAGNOSIS

Freeman⁶ calls attention to the value of the Roentgen ray in intrathoracic lesions in childhood. It is a useful aid to auscultation and percussion in clearing up the diagnosis of doubtful conditions. The Roentgen ray has its greatest value in tuberculosis, and in pneumonia without physical signs. In cardiac lesions it gives information as to the size and shape of the heart and the presence of exudate in the pericardium. In the case of a child with an elevated temperature with sibilant, sonorous, or crepitant râles through the lungs, and positive

4. Peiper, E.: Deutsch. med. Wchnschr., 1916, pp. 213 and 245.

5. Miller, J. A., and Noble, W. C.: Jour. Exper. Med., 1916, xxiv, 223.

6. Freeman, R. G.: Arch. Pediat., 1915, xxxii, 891.

von Pirquet, it is impossible to distinguish a bronchitis with small latent focus of tuberculosis from a case of miliary tuberculosis. The Roentgen ray is the only means at our command for making this diagnosis.

It is extremely valuable, also, for distinguishing effusion from consolidation, pneumothorax, etc. The thymus, bronchial and mediastinal lymph nodes often cast shadows, making a diagnosis possible. Freeman reports a case of pneumonia without physical signs, one with pericardial effusion, and a case of endocarditis in which the size of the heart showed the effect of rest and treatment.

ASTHMA

Cameron⁷ believes that asthma is a respiratory neurosis. In children it is characterized more by the bronchitic than by spasmodic symptoms, and it is often impossible to determine whether a given attack is asthmatic or not by the physical signs. The following points suggest asthma:

1. Family history of asthma, gout or migraine.
2. Exudative diathesis (eczema, seborrhea, urticaria).
3. Eosinophilia.

Cameron believes that psychological treatment is very important, and that every effort should be made to avoid frightening the child during the paroxysm by overanxiety on the part of the parents. During an acute attack the room should be brightly lighted and the child should be diverted if possible by books or toys. A hot bath or an emetic sometimes relieves the attack. Chloral or atropin are considered the best drugs.

He advises a diet largely of fruits, vegetables and cereals, avoiding eggs and milk, and giving meat in small amounts only once a day. Adenoids should be removed if present. Fresh air and vigorous exercise are important. Potassium iodid should be administered. In infants treatment must be directed toward the bronchitis by confinement to the room, steam, counterirritation, etc.

Jackson⁸ describes the manner in which drugs act in relieving asthmatic attacks. He divides their mode of action into two groups.

The first group acts by paralyzing the endings of the bronchoconstrictor nerves to the muscle fibers of the bronchioles, causing a relaxation of the bronchioles. To this group belong atropin, hyoscin, etc.

The second group acts by stimulating the endings of the bronchodilator nerves. This is the way in which epinephrin and allied drugs act.

7. Cameron: *Guy's Hosp. Gaz.*, 1915, xxix, 319.

8. Jackson, D. E.: *Jour. Lab. and Clin. Med.*, 1915, i, 126.

It is probable that two forms of the disease may exist. These can be demonstrated experimentally. From clinical evidence it may be that these two forms may exist separately or at the same time.

The first form is due to nervous influence, central, peripheral or reflex. Nervous impulses arising from direct central influence or reflexly excited (as by a nasal sinus disease) pass down the bronchoconstrictor nerves and stimulate the muscles to contract. Possibly chemical substances in the blood may stimulate these endings directly or by acting on the ganglia in their course. We know of no such substances produced in the body, but experimentally arecoline will cause bronchoconstriction which is relieved or prevented by atropin.

The second form is due to direct stimulation of the muscle fibers of the bronchus. It may be produced experimentally by enormous doses of atropin or hyoscin. It is very evident that atropin will do no good in this type of the disease. Epinephrin relieves it by stimulating the bronchodilator endings which the atropin has not affected.

A considerable number of drugs will cause direct muscular spasm independent of innervation; for example, morphin, codein, heroin, narcotin, some of the metallic salts. A spasm caused by these drugs is more lasting than that due to the nervous form of asthma and more difficult to treat by the drugs acting on the bronchodilators.

Guinea-pigs with anaphylactic shock die chiefly from constriction of the bronchi. Atropin is of slight value in these cases, much less so than a full dose of epinephrin. It has been suggested that the substance formed in anaphylaxis is histamin or some related substance. Histamin is formed from histidin by certain bacteria. In animals histamin causes bronchoconstriction of a severe type which yields but slightly to atropin. It is possible that histamin or some related substance may be the cause of asthma in man.

Pilocarpin causes great bronchoconstriction by stimulation of the peripheral nerve endings. It is difficult to see how this drug can relieve asthma, although it has been said to do so in some cases. Possibly it does so by stimulation of the adrenal to increased secretion, and this may explain a paradoxical bronchodilatation.

BACTERIOLOGY OF NASAL INFECTIONS

Foster⁹ points out that a great variety of organisms have been thought to be the cause of a common cold in the head. He has repeated Kruse's experiment with Berkefeld filtrates from the discharges of coryza. The discharges were mixed with salt solution and passed through a Berkefeld filter. The filtrate was sterile on ordinary culture

9. Foster: Jour. Am. Med. Assn., 1916, lxvi, 1180.

mediums, both aerobic and anaerobic. Ten soldiers were inoculated by dropping this clear filtrate into their noses, and nine developed typical colds in the head. Foster applied the culture methods developed by Noguchi and others, using rabbit kidney and ascitic fluid covered with oil. With this medium and the above filtrate he obtained a cloudiness around the pieces of tissue which was not obtained in controls and the repeated subcultures gave the same findings. The cultures under the dark field microscope showed small globular bodies which were apparently motile, and these were also seen in stained smears. The filtrates from these subcultures were also clear, and sterile with ordinary culture methods. When inoculated into the noses of eleven patients they produced acute coryza, and cultures from the discharges of these cases on ascitic tissue mediums gave the same clouding of the fluid around the pieces of tissue which were observed in the original cultures.

Baxter¹⁰ made a study of sixty cases of postnasal infection in childhood, which was very prevalent in the earlier part of 1915. It was nearly all due to staphylococcus. The middle ear was involved in 75 per cent. of the cases, and this was especially common under 2 years of age. There were few other complications except cervical adenitis.

Baxter advises nasal douches with gravity pressure and the use of sodium bicarbonate or citrate, internally. He thinks that one should not be too hasty in puncturing the membrana tympani, since many cases will subside without puncture under irrigations with bicarbonate or boric acid solutions.

INFLUENZA

Leo-Wolff¹¹ distinguishes between influenza which is an acute infectious epidemic disease, due to *Bacillus influenzae*, and grip or grippy colds, due to pneumococcus, streptococcus, *Micrococcus catarrhalis* or Friedländer's bacillus. He believes that climatic changes, exposure to cold, or anything that lowers the vitality of the patient, predisposes to both. The mode of transmission is usually through sneezing, coughing, etc. In hospitals, epidemics may be averted or minimized by the exclusion of visitors, the wearing of gauze masks by doctors or nurses having colds, and by the separation of infants by gauze screens.

He calls attention at the fact that influenza often simulates measles, scarlet fever, meningitis and digestive disturbances in infants, and that sporadic cases are very difficult of diagnosis in such atypical cases. A general discussion of the two groups above mentioned brings out nothing of great value.

10. Baxter, G. E.: Arch. Pediat., 1916, xxxiii, 729.

11. Leo-Wolff: Med. Rec., New York, 1916, lxxxix, 226.

PNEUMONIA

In a preliminary report of 1,000 cases of pneumonia Pisek and Pease¹² have found a mortality of 34.3 per cent.

In 445 cases of bronchopneumonia the mortality was 41 per cent.

In 227 of lobar pneumonia the mortality was 28.1 per cent.

Of the bronchopneumonia patients, the greater proportion were under 2 years of age. The mortality was 52 per cent. in the first year, and there were no deaths over 3 years.

Of the lobar pneumonia, while there was a larger percentage of the cases above 2 years of age, there was still a considerable number under that age (seventy-five in the first year and ninety-seven in the second year).

There was noted a marked difference in the variation of mortality in the epidemics of different years. The bacteria found in the lobar pneumonia cases were pneumococci with a few staphylococci and streptococci. In bronchopneumonia, streptococci, staphylococci and influenza bacilli predominated. Pneumococci with streptococci and staphylococci were also found, that is, mixed infections, and in these cases the pneumococci were usually of a low grade of virulence.

The character of the infection depended on the amount of natural or acquired resistance of the patient, the state of his vitality, local changes in the respiratory tract and the virulence of the organism.

Forty-eight cases were studied according to the type of the pneumococcus with the following results:

	Lobar	Broncho	Deaths	Death Rate
Type I	9	2	1	22.9
Type II	11	3	5	29.3
Type III	1	3	1	8.3
Type IV	7	12	4	39.8

Wollstein and Benson¹³ have studied the organisms present in pneumonia in children in fifty cases to determine the type of pneumococcus present. They found Type IV in 60 per cent. of the cases, usually associated with one of the other types. The mortality was 40 per cent.

In Type I the mortality was 83 per cent., and in Type II, 33 per cent. This differs from the findings in adults in whom Type II has a higher mortality than Type I, and in whom Type IV is not often fatal.

Dunn and Hammond¹⁴ report a case of pneumonia in a child of 14½ months, due to Friedländer's bacillus. The left lower lobe was involved, then the left upper lobe. Thoracentesis was performed on account of persistent temperature and signs at the base, and a small

12. Pisek, G. R., and Pease, M. C.: *Am. Jour. Med. Sc.*, 1916, cii, 14.

13. Wollstein, M., and Benson, A. W.: *AM. JOUR. DIS. CHILD.*, 1916, xii, 254.

14. Dunn, C. H., and Hammond, J.: *Interstate Med. Jour.*, 1915, xxii, 1133.

amount of fibrinous material was withdrawn from the lung. This gave a culture of Friedländer's bacillus, and this finding was confirmed by a second puncture. The fever persisted for eighteen days and the temperature dropped by crisis. The child made a good recovery. The case was reported in detail on account of the rarity of recovery from an infection with this organism.

Perrot¹⁵ considers facial herpes in pneumonia or pneumococcal infections to be always a localization in the skin or mucous membrane of the pneumococcus, which is always found in the contents of the vesicle.

Herpes is often the principal manifestation of pneumococcal infection, the signs of pneumonia being ill-marked or absent. The same is true of pneumococcal septicemia, stomatitis, angina or meningitis. Infection of the skin probably takes place through the blood stream. He gives several illustrations of cases in which the herpes is the main feature of the infection.

Mason¹⁶ confirms the findings of Weill and Mouriquand that central pneumonia does not exist; that the shadow cast by a pneumococcal consolidation is triangular in shape, the base in the axilla, the apex toward the hilum. When the apex of the bronchial shadow does not extend to the root of the lung, bronchial voice and breathing are not heard. As soon as the consolidation extends far enough to come in contact with the large bronchi at the hilum, bronchial voice and breathing are heard.

This gives a most reasonable explanation for the absence of physical signs in the early stages of consolidation and can be easily verified in any case in which daily roentgenograms are taken.

Hutinel¹⁷ considers that pulmonary complications are not rare in scarlet fever, which is contrary to the usual opinion. In five years he observed 2,500 cases of scarlet fever, and one-third of the deaths were from pneumonia. These occurred in three forms: bronchopneumonia, lobar pneumonia and congestive pneumonia or pseudo-lobar bronchopneumonia.

Bronchopneumonia is frequent in small infants in severe cases with purulent rhinitis, otitis, severe angina, etc. It is streptococcal in origin and is an extension from the infection of the upper air passages. Deformities of the chest from rickets and Pott's disease predispose to pneumonia. The most severe cases are those associated with measles following scarlet, or when the pneumonia appears in an epidemic form among a group of children in a scarlet ward. These facts are well

15. Perrot, J.: Thèse de Lyon, 1913-1914, No. 130; abstr. in *Brit. Jour. Dis. Child.*, 1916, xiii.

16. Mason, H. H.: *AM. JOUR. DIS. CHILD.*, 1916, xi, 188.

17. Hutinel, V.: *Arch. de méd. d. enfants*, 1916, xix, 57.

known, but the frequency of pneumonia is commonly underestimated, being overlooked in children who are gravely ill. If its occurrence is not borne in mind it will only be found on the necropsy table.

Lobar pneumonia occurs in three groups according to the time of its onset. Hutinel has called certain of these cases "pneum scarlatina," which he considers comparable to cases of pneumotyphoid.

He differentiates three groups as follows:

1. The pneumonia precedes scarlet by several days.
2. The pneumonia comes on during the course of scarlet.
3. The pneumonia comes on during convalescence.

In the first form the ordinary symptoms of the pneumonia exist, and the appearance of the scarlet rash comes as a surprise. It is difficult to determine whether the rash is toxic in origin or true scarlet. The pneumonia is probably not due to the scarlet, but is an ordinary pneumococcus infection. The appearance of the scarlet does not change the diagnosis; it is merely a superadded infection. It can be determined that it is a true scarlet from the course and symptoms. The red throat, tongue, cervical adenitis, desquamation and late complications are those of scarlet. The two infections modify each other, however, and resolution is usually slower than in an ordinary pneumonia. Pleural reactions are nearly constant.

The pleurisy may be serofibrinous or a simple parapneumonic, non-infectious effusion, but usually becomes purulent. It may be due to streptococcus or pneumococcus. Some cases show pneumococcus in the sputum and streptococcus in the effusion. The prognosis is doubtful. Some patients recover, but with slow convalescence, often protracted by the late complications of scarlet.

Relapses of the scarlet fever seem to be abnormally frequent, following these cases, and may come on as late as sixty to seventy days after the original infection.

The second group, in which the pneumonia appears during the acute stage of the scarlet, is divided into two subgroups:

(a) In the first subgroup the pneumonia appears at the same time as the rash. It is contemporaneous with the angina, usually apical, and is sometimes mild and sometimes fatal. It resembles in its characters ordinary lobar pneumonia.

(b) In the second subgroup the pneumonia appears after the eruption has existed several days. It is usually at the bases, bilateral, and resembles bronchopneumonia. It is commonly a streptococcal infection and the prognosis is usually grave.

The pleural reactions are frequent, and vary from a transient clear effusion to an empyema of a severe type. The scarlet symptoms rarely predominate, but are generally of subsidiary importance.

The third group comprises pneumonias occurring during convalescence. These are accidental pneumococcus infections. They are not very rare and the prognosis is usually good. Pleural complications are frequent, however, and they seem to predispose to relapses of the scarlet in the same manner as the first group. In the cases complicated by empyema, prognosis is less good, 30 per cent. being fatal.

Hutinel concludes that in pneumonia and scarlet occurring together, the infections are apt to aggravate each other; the pneumonia is influenced more than the scarlet, and its prognosis is much less favorable than in an uncomplicated pneumonia. The pleural complications are frequent, varying from a mild serous effusion to severe empyema. Relapses occur in one third of the cases complicated by pneumonia. This is very much more common than in uncomplicated scarlet, in which relapses occur in not more than 1 per cent. Hutinel suggests the possibility that pneumonia modifies the effort of the organism acquiring immunity, and so makes reinfection with scarlet more common. This paper is illustrated by many cases reported in detail.

Toupance¹⁸ considers that the respiratory complications of scarlet fever are less rare than the textbooks usually state.

He has found laryngitis in 5 per cent. of the cases, due to streptococcus. In young children it is usually fatal.

Bronchitis occurs in 2 to 6 per cent. It is commonly mild and always suggests the possibility of measles.

Bronchopneumonia is found in 1 to 2½ per cent. of hospital cases, usually accompanying severe infections of the nasopharynx or general sepsis. The mortality is 50 per cent.

Lobar pneumonia was found in 1 per cent. of the cases. It may coincide with the onset of the scarlatina and the two diseases run their course without effect on each other. Relapses are common in such cases. When it occurs during the eruptive or desquamative stages it tends to affect the apex of the lung and often runs a torpid form which is difficult of recognition. It is frequently accompanied by pleural effusion.

Pleurisy is found in 0.8 per cent. of the scarlatina cases; two thirds of these are purulent.

Of the empyema observed, some cases have been generalized, some have been "latent" (bronchopneumonia with interlobar effusion); all have been characterized by rapid pus formation, abundant effusion, and grave general condition. The death rate was 40 per cent.

Serofibrinous pleurisy has usually been of streptococcus origin. It may be associated with foci of pulmonary congestion or complicated by pericarditis or tuberculosis.

18. Toupance, M.: Thèses de Paris, 1914-1915, No. 80.

Allan¹⁹ reports a case of a child with abdominal symptoms indicating acute appendicitis. Operating on the sixth day of the disease, the appendix was found to be inflamed, contained a blood clot and several thread worms. The anesthetic was chloroform-ether. A cough developed the day after the operation and signs of consolidation were discovered at both bases. Two days after the operation, the eighth day of the disease, the temperature, which had been persistently high, fell by crisis. The case is remarkable on account of the definite inflammation of the appendix in a case of pneumonia, showing it was not an ordinary case of pneumonia with abdominal signs.

Caillé²⁰ reports three cases of foreign-body pneumonia. The first was a child of 2 years and 10 months who had been sick for four weeks with fever and chills and vomiting followed by dyspnea. There were purulent sputum and leukocytosis, with dulness at the base of the right posterior chest. The Roentgen ray showed a tack in the bronchus, which was removed by a bronchoscope guided by the fluoroscope.

The second was a child of 2 years who had had pneumonia the year before, following which there was persistent cough and physical signs (flatness over the chest, bronchial breathing and râles). The Roentgen ray showed a nail in the left bronchus and trachea. An effort was made to remove this with the bronchoscope, but this was unsuccessful. A second attempt through a tracheotomy wound was successful, but pneumonia resulted and the child died.

The third was a 4-year-old child who swallowed a shawl pin three days before admission. The Roengen ray showed the pin to be in the left bronchus. An attempt was made to remove the pin, but this was unsuccessful and following this there was a fever which lasted two weeks. The pin was finally coughed up forty-three days after it was swallowed.

Caillé emphasizes the importance of using the Roentgen ray in unresolved and atypical pneumonia. He urges that all foreign-body cases be reported in the lay press as a warning to parents to keep objects which might be inhaled or swallowed out of the reach of small children. The indirect suggestion offered children by seeing parents put things in their own mouths may lead to imitation by the children. It should, therefore, be avoided.

Clarke²¹ reports his experience in about thirty cases of pneumonia treated with hexamethylenetetramin. In every case except one the temperature started to fall a few hours after beginning the drug, and in

19. Allan, J.: *Brit. Jour. Child. Dis.*, 1916, xiii, 207.

20. Caille, A.: *Arch. Pediat.*, 1915, xxxii, 881.

21. Clarke, T. W.: *New York State Jour. Med.*, 1915, xv, 445.

every case the patient became well in twenty-four to forty-eight hours. The drug was given in most cases during the first four days of the disease. There was one bronchopneumonia resulting in death in an infant of 4 months.

Whenever a child has failed to respond in forty-eight hours he has always been able to find a complication. He also has given the same remedy in influenza, measles and pertussis and has had no pulmonary complications. He pushes the drug to the limit of tolerance, well diluted in water or milk. Occasionally strangury or hematuria results, in which case the drug is discontinued and sodium bicarbonate given.

In a clinical lecture on the treatment of bronchopneumonia, Marfan²² advises that the sick-room should be kept at 62 F., with free ventilation, but avoiding chilling the patient. The child's position should be changed frequently to avoid congestion at the bases.

Nasal catarrh should be treated by instillations of eucalyptol in oil, 1 to 6, or collargol, 1 per cent.

If there is no digestive disturbance, the child should be fed "as in any other febrile state with equal parts of milk and sweetened water."

He differentiates four forms of the disease, acute, hyperacute (capillary bronchitis), subacute, and latent. He advises counterirritation by hot baths at 100 F. every three hours when the temperature reaches 102.5. These provoke vasodilatation, relieve the dyspnea and promote sleep. Wet packs at 80 F. can be given from the arm pits to the umbilicus for one and a half hours. The nondepressing expectorants such as ergotin and nux vomica may be used.

In influenzal cases he recommends inunctions of collargol, 3, lanolin and petrolatum of each, 10 parts.

In the suffocation attacks of the hyperacute form, mustard baths or mustard packs should be used and stimulation with camphor, caffeine and oxygen are necessary.

COLD AIR IN TREATMENT

Morse²³ differentiates between the value of fresh air and cold air in the treatment of respiratory infections in childhood. Discomfort in a closed room is not due to expired poisons, but to warmth, moisture and stagnation of the air. Fresh air is air that is cool, dry and in motion. Dust is undesirable.

It is possible to lay down the following rules from clinical experience:

In nasopharyngitis cold air is irritating in the early stages and predisposes to otitis. Fresh air is of advantage, but it should be warm.

22. Marfan, A.: *Med. Press and Circular*, 1915, c, 408.

23. Morse, J. L.: *Jour. Am. Med. Assn.*, 1916, lxxiii, 375.

The child should be kept in a room at a temperature not below 60 F., if he is kept in bed, or 65 to 66 if out of bed.

In laryngitis, cold air is very irritating in the early stages, but has no effect later. Patients are more comfortable if the air is moist, and at about 70 F.

In acute bronchitis the cough and sternal oppression are increased by cold air in the beginning of the disease. Children should be kept at a temperature of 60 to 70 F., and the air should be moist. In later stages cold air is less irritating, but has no advantage over warm air. It is no longer necessary to have the air moistened, as the mucous membrane of the bronchi is covered with secretion.

In bronchopneumonia the acute stage of the bronchitis is usually passed, and hence there is no contraindication to the use of cold air.

In lobar pneumonia there is usually no bronchitis and here cold air has its greatest value. There is no question that the general stimulating effect of the cold is of great advantage. The patients are much more comfortable, but the available statistics show but little difference in the mortality in children treated in cold air.

Freeman²⁴ believes that the pediatricist has a powerful therapeutic agent in moving, cool outdoor air. It stimulates the appetite, induces quiet sleep, brings color to the cheek, increases the resistance to infection.

Howland and Hoobler's observation that the blood pressure is raised by a change from a warm room to cold air has not been confirmed by later observers, and so the good results cannot be attributed to the effect on the circulation. The favorable action of fresh air is probably due to the absence of the depressing effect of the air in closed rooms. It has been shown that this is not due to diminished oxygen or increased carbon dioxide in the air, but to the fact that stagnant, warm, moist air prevents cooling of the body. In cool fresh air the body can cool itself more easily. Outdoor porches are best in the treatment of sick children and are probably applicable to all infectious diseases except possibly scarlet and measles. Fresh air finds its greater use in pneumonia and tuberculosis. The best substitute for the sleeping porch is a room with cheese cloth screens in the windows.

Premature infants should be kept in air which is warm enough to keep up the body temperature, but it should be freely moving warm air, not stagnant.

In renal and cardiac cases the value of cold air is doubtful. Freeman believes that parents and children should be thoroughly trained to the value of fresh air and away from the idea of the harmfulness of drafts.

24. Freeman, R. G.: *Arch. Pediat.*, 1916, xxxiii, 330.

Cunningham²⁵ has analyzed 1,500 cases of pneumonia treated in the Children's Hospital in Boston. Two hundred of these patients were treated prior to 1906 in a fairly well ventilated ward. After 1906 all patients were treated out of doors. Cunningham concludes that the results of open air treatment have not come up to expectation and that the death rate is slightly higher than before the cold air treatment was instituted. The patients were formerly treated in a ward which was well ventilated with a good grade of fresh air, although it was warm. Empyema has been slightly more frequent under the cold air treatment. Before 1906 the duration was 9.1 days. Since then under the cold air treatment it has been 8.7 days.

These statistics are interesting in view of the almost general use of cold air in treatment of pneumonia.

Freeman,²⁶ on the other hand, states that it is an accepted fact that fresh air increases the appetite and digestive power, and in spite of its doubtful effect on the blood pressure he believes that fresh air is of the greatest value. In his twenty-five cases of lobar pneumonia there were only 12 per cent. of deaths, and in the uncomplicated cases only 4.7 per cent. In sixty-two cases of bronchopneumonia there were 16 per cent. deaths and in the uncomplicated only 3.3 per cent.

Morse and Hassman²⁷ have made a large number of blood pressure readings on children with pneumonia in an attempt to verify the work of Howland and Hoobler. They found that the temperature of the surrounding air had no effect on the systolic, diastolic and pulse pressures. The temperature of the surrounding air seemed to affect the pulse rate, however, the pulse being lower out of doors than in the ward. The same is true of the rate of respiration, although there were many exceptions to both of the latter observations.

The general impression of the physicians and nurses was that the children were more comfortable outdoors than in the ward. They coughed less, were quieter, had a better color and took their food better out of doors.

No conclusions are justified at present as to the effect of the cold air treatment on the mortality in pneumonia.

PLEURA

Gittings, Fetterolf and Mitchell²⁸ have found that the fissures of the lungs show practically the same relation to the bony framework of

25. Cunningham, A. R.: *Boston Med. and Surg. Jour.*, 1916, clxxiv, 753.

26. Freeman, R. G.: *Am. Jour. Med. Sc.*, 1916, cii, 1.

27. Morse, J. L., and Hassman, D. M.: *AM. JOUR. DIS. CHILD.*, 1916, xii, 445.

28. Gittings, J. C., Fetterolf, G., and Mitchell, A. G.: *AM. JOUR. DIS. CHILD.*, this issue, p. 579.

the chest in infants as in adults. The variations are considerable, but do not depend on any anatomic character of the chest, and therefore cannot be predicted from the shape of the chest. The lower level of the lungs is not quite so low as in adults, and hence great care must be taken to avoid injury to the diaphragm in thoracentesis. The lowest safe point is in the fifth or possibly the sixth space in the midaxillary line, and the seventh or possibly the eighth space in the line of the angle of the scapula. The optimum point of puncture is the seventh space in the posterior axillary line.

Bayne-Jones²⁹ reports a case of pleural eosinophilia following pneumonia. The case presented no unusual features and was a pneumococcus infection of Type II. It was followed by pleural effusion. The fluid was sterile. It contained 580 to 600 cells, of which 6 per cent. were polymorphonuclear and 45 per cent. eosinophils. The blood contained only 1.2 per cent. eosinophils. Pleural eosinophilia is a comparatively rare condition, but is probably more common than is usually thought to be the case on account of the failure to stain the smears with polychrome stain. Bayne-Jones has found an incidence of from 1 to 5 per cent. of a series of patients who were examined carefully in regard to this point. It has been reported in eight cases following a lobar pneumonia. It has been found in a long line of diseases, including practically every cause of pleural effusion. There is no relation to the cytologic formula of the other cells in the fluid, or to its sterility. It has no diagnostic significance except that the effusion is usually non-tuberculous. The prognosis is good, since these effusions are nearly always transient and benign. The only explanation offered is that it is possibly a local anaphylactic reaction, from the splitting of the proteins occurring during the process of resolution and absorption.

EMPHYEMA

Brown³⁰ says that the recognition of pleural disorders by the Roentgen ray is rendered difficult by the fact that in acute pleurisy, especially if complicated by pneumonia, the patient cannot be brought to the Roentgen-ray plant. A portable outfit is necessary and the portable fluoroscopic outfit is simpler than that necessary for the making of plates. In the acute stage the fluoroscope detects changes from the normal physiologic motion of the lung. In the subacute and chronic cases of chronic adhesive pleurisy, after operation for empyema the Roentgen ray determines the amount of thickening of the pleura and the amount of available lung tissue beneath. These facts are more difficult to determine by ordinary physical examinations.

29. Bayne-Jones, S.: *Bull. Johns Hopkins Hosp.*, 1916, xxvii, 12.

30. Brown, P.: *Boston Med. and Surg. Jour.*, 1915, clxxiii, 804.

It is possible by the Roentgen ray to watch the expansion of the lung damaged by an empyema, and it is especially gratifying to observe the results of treatment.

Gorter³¹ reports two cases of interlobar empyema cured by a simple puncture. The first was a child of 15 months who had had fever for five months, following measles and bronchopneumonia. The child had cough constantly and had difficulty in breathing, anorexia and loss of weight. On examination the child was thin, pale and dyspneic. The lungs showed dulness in the right interscapular region which extended downward obliquely to the right and reached the liver dulness in mid-axillary line. Over this area there was tubular breathing and moist râles. The Roentgen ray showed a corresponding shadow. Leukocytes, 24,000. Puncture in the sixth space withdrew, at a depth of 4 cm., 10 c.c. of greenish pus containing pneumococci. Following this there was a rapid recovery and the disappearance of the sign.

The second case was in an infant of 5 months who in the course of pertussis had bronchopneumonia lasting fifteen days. One month later a fever of intermittent type was noted, caused by purulent pleurisy on the right side. Eighty cubic centimeters of pus were withdrawn and a staphylococcus was found. The temperature continued after this, running from 99 to 102 F. Twenty days after the first puncture examination showed a normal lung at the apex and base, but dulness and tubular breathing in the interscapular region. The Roentgen ray showed a shadow which corresponded to this. Von Pirquet negative. Puncture of the sixth space in the scapular line permitted withdrawal of 10 c.c. of pus at a depth of 6 cm. After this the temperature fell gradually and the signs disappeared. Gorter explains the good effects in interlobar effusions by the relaxation of the tension in the sac caused by withdrawing the fluid. These effusions are usually well walled off from the general pleural cavity, and if recognized, the prognosis is good.

Gerdine³² made a study of pleural effusions occurring during the acute stage of pneumonia. In six out of fifteen cases the fluid was discovered before the crisis. Most of these fluids were sterile, slightly turbid, containing a large number of leukocytes, mostly polymorphonuclear.

He believes that this type of parapneumonic empyema is usually, but not always, of a benign type, that it occurs frequently, and can be demonstrated by the Roentgen ray, physical signs or puncture. It does not alter the course of the pneumonia. True pus is present more rarely and may contain virulent organisms. The degree of virulence of the organisms, determined by animal inoculations, seems to be of prog-

31. Gorter, E.: *Arch. de méd. d. enfants*, 1916, xix, 317.

32. Gerdine, L.: *AM. JOUR. DIS. CHILD.*, 1915, xi, 33.

nostic value. Surgical interference should only be considered when the organisms found are of high virulence.

It is evident that operation on a child with pneumonia who has a small collection of sterile fluid in the pleural cavity is not justifiable. Operation should be postponed until after the crisis of the pneumonia, unless the amount of pus is large or the organisms are virulent.

Bertoldi³³ reports two cases of pyopneumothorax in infancy. The first was in a child of $3\frac{1}{2}$ years who was found to have signs of pyopneumothorax, was operated on and died. Necropsy showed a foreign body at the bifurcation of the left bronchus, bronchopneumonia and a small abscess, with a perforation of the pleura. The second case was a 15 months' infant who had a pneumococcus infection resulting in pyopneumothorax and death. The diagnosis was made by the Roentgen ray. Bertoldi advises operation as the only hope in these cases, but only in the nontuberculous variety.

In discussing the pneumodynamics of empyema, Cotton³⁴ says that the intrapleural pressure is determined by the positive pressure in expiration and the negative pressure in inspiration, the elasticity of the lung, lymphatic absorption, and the surface tension of the great pleural surfaces tending to preserve contact of the lung with the chest wall. The last factor is sufficient in itself to prevent collapse of the lung if the pleura is only slightly torn. With larger wounds the lung contracts unless held by adhesions. When a chest full of fluid is opened the lung does not collapse at once. On the contrary, the fluid is expelled in a jet. This is caused by the cough excited by the pleural reflex. The lung usually expands at first but collapses within a few hours. With a proper dressing the lung does not collapse at all, and therefore in a double empyema a proper valve dressing makes it possible to operate on both sides at the same time. The factors determining lung collapse are the previous collapse and lung compression by the fluid, free access of air, respiration with partial closure of the glottis and an accidental valve action at the wound. Cotton believes that any positive pressure apparatus is dangerous, since this is not the proper way to expand the contracted lung.

Proper drainage is the most important factor and is the true way to prevent collapse. It is important to remove the fibrin masses at the time of an operation to prevent plugging of the tube. The rib resection must be one-half to three-fourths of an inch long so that the finger may be inserted and the fibrin swept or fished out. The patient may be turned so that the wound is directed downward, and coughing will

33. Bertoldi, M.: Thèse de Buenos Aires, 1915; ref. in *Arch. de méd. d. enfants*, 1916, xix, 167.

34. Cotton, F. J.: *Boston Med. and Surg. Jour.*, 1916, cixxiii, 804.

often expel the fibrin. Cotton believes that irrigations are dangerous and should not be used. Drainage is promoted by whatever best aids expansion of the lung. Most cases of empyema get well by accident, because the wet, pus-soaked dressing acts as a fair valve. Cotton uses a square of rubber tissue held taut at the corners by adhesive strips. A little glycerin is run between this and the chest wall. The drainage tube is put through a tight opening in the center of this and negative pressure is applied by means of a column of water which causes a suction through an arrangement of bottles. The water column should not be over 10 inches high, since a stronger suction than this is dangerous and may cause pleural hemorrhage. Blow bottles are very useful to promote expansion of the lung. Decortication operations are rarely necessary.

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